

An Investigation of Episodic Foresight Ability in Users of Illicit Substances

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'I'm sure mine only works one way,' Alice remarked.

'I can't remember things *before* they happen.'

'It's a poor sort of memory that only works backwards,' the Queen remarked.

- Lewis Carroll

Abstract

The overall objective of this research project was to investigate the cognitive ability of episodic foresight in various drug-using populations. Episodic foresight refers to the uniquely human ability to mentally project the self into the future and pre-experience an event. The first study (in press) was designed to address an identified gap in our understanding of episodic foresight in long-term opiate users. A group of long term opiate users ($n = 48$) and a group of matched controls ($n = 48$) were compared on episodic foresight, and the contribution of memory and executive function to this ability were investigated. The results of the first study identified specific episodic foresight impairment in the context of chronic opiate use which was not secondary to memory or executive control processing. Given these findings and recent literature that has begun to explore the cognitive and neural underpinnings of episodic foresight, the primary objective of the second study was to explore whether the deficit in episodic foresight among long-term opiate users identified in Study 1 may be attributable to compromised scene construction and/or self-projection abilities, both of which have been implicated in similar deficits observed in other clinical samples. This study assessed a group of long-term opiate users ($n = 35$) and demographically matched controls ($n = 35$). The results confirmed the episodic foresight deficit, and identified a specific impairment in self-projection. The third study aimed to assess whether an episodic foresight deficit would be observed in substance users at the less severe end of the spectrum of substance use. The third study assessed recreational cannabis users ($n = 25$) and demographically matched controls ($n = 45$). The results indicated no episodic foresight impairment in this group. Overall, the results of this research project suggest that compromised episodic foresight is apparent in the context of chronic but not recreational substance use. A

breakdown in episodic foresight may therefore represent an important potential mechanism that may contribute to the poor functional, social, and treatment outcomes often associated with chronic substance use.

Declaration.

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or other institution and, to the best of my knowledge and belief, it contains no material previously published or written by another person, except where due reference is made.

The ethical principles and procedures specified by the Australian Catholic University's policy document on Human Research and Experimentation have been adhered to in the preparation of this report

Signed

Date

Acknowledgments

I feel that it is only fitting that my acknowledgements are as epic, in size and emotion, as the thesis journey I have just survived...

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CHAPTER 1: Introduction and Thesis Outline

1.1 Introduction

Substance abuse can severely impact the life of the using individual, and can also place significant socioeconomic strain on wider society. The most recent data on the cost of substance abuse (both licit and illicit) to Australian society estimated it to be \$55.5 billion in the 2004/05 financial year (Collins & Lapsley, 2008). Illicit substances alone accounted for \$8.2 billion of this estimate, which incorporate costs related to crime, healthcare, labour productivity (at home and in the workplace), fire, and road accidents. This estimate not only highlights the detrimental outcomes associated with substance abuse, but also reinforces the importance of prioritising this issue in various areas of research and policy development in order to prevent or reduce such devastating outcomes for individual users and society as a whole.

Obtaining epidemiological data regarding substance use is a difficult task because in many countries the use of psychoactive substances is illegal and not all nations conduct regular national investigations into drug use trends. However the most recent prevalence estimates of global illicit drug use suggest approximately 5.2 per cent (243 million) of the population aged between 15 – 64 years are using illicit drugs (United Nations Office of Drugs and Crime, 2014). Overall, global illicit substance use increased between 2009 and 2012 with this being attributed to not only the increase in the worldwide population but also to an increase in substance use behaviour. Cannabis continues to be the most commonly abused substance worldwide (3.8%), with prevalence estimates showing a steady increase between 2009 and 2012 (United Nations Office of Drugs and Crime, 2014). This is followed by the use of opioids (0.7%), amphetamine-type stimulants (0.7%), opiates (0.4%), cocaine (0.4%), and ecstasy (0.4%) (United Nations Office of Drugs and Crime, 2014). In Australia alone, the

results of the most recent National Drug Strategy reported that 14.7% of the adult population (individuals aged 14 – 64 years old) had used some type of illicit substance in the twelve months prior to the survey (Australian Institute of Health and Welfare, 2011). This was a 1.3% increase from the previous report in 2007. Similar to worldwide trends, cannabis is the most widely used illicit substance among Australians (10.3%), but this is followed by ecstasy (3%), amphetamine-like stimulants (2.1%), and then cocaine (2.1%) (Australian Institute of Health and Welfare, 2011). Opiates such as heroin are relatively low in national prevalence (0.2%) (Australian Institute of Health and Welfare, 2011) but more deleterious outcomes are associated with opiates than more commonly used substances such as cannabis (United Nations Office of Drugs and Crime, 2014).

Irrespective of legality and variations of use, substances of abuse alter mood, cognition and behaviour by disrupting neurological functioning within the central nervous system. This can occur via two methods. The first is by the imitation of endogenous neurotransmitter systems, and the second is by overstimulation of the neurological circuits related to reward. Psychoactive substances are classified based on the nature of their neurological influence. Drugs such as alcohol, cannabis, opioids, and opiates exert their influence by depressing central nervous system functioning and are therefore classified as ‘depressants’. Amphetamine-type stimulants such as amphetamines (ecstasy, speed), methamphetamines (ice, crack, crank) and 3,4-methylenedioxymethamphetamine (MDMA; a derivative of ecstasy), and cocaine accelerate central nervous system functioning and thus are classified as ‘stimulants’. Many drugs of different classifications target similar neural regions but different neurocognitive outcomes can present given the variations in psychoactive properties between substances. Regardless of the nature of the substances, the associated neurological disruption is reflected in behavioural and cognitive changes, repeated relapses, as well as intense cravings when the individual is presented with substance related stimuli.

However, not all use of psychoactive substances would be classified as problematic. Rather, substance use varies along a spectrum of severity depending upon frequency, duration and impact of use. General diagnosis of substance use disorders is related to the pathological behaviours surrounding the use of any particular substance (American Psychiatric Association, 2013). There are four groupings of pathological behaviours used in this diagnosis. The first criteria is related to impairments in control over the substance of choice; the second relates to social impairments as a result of substance use; the third concerns engagement in risky behaviours in the attainment and use of the substance; and lastly pharmacological effects of withdrawal and tolerance. Research has demonstrated that these presentations are reflections of underlying neurocognitive dysfunction (Baler & Volkow, 2006; Goldstein & Volkow, 2002; Volkow & Fowler, 2000).

1.2 Introduction to cognitive functioning in substance use

Despite the heterogeneous nature of substance-using populations, many cognitive neuroscience oriented studies have highlighted the deleterious effects of illicit drug use on cognitive processing abilities (De Sola Llopis et al., 2008; Elmer et al., 2006; Fernández-Serrano, Pérez-García, & Verdejo-García, 2011; Fernández-Serrano, Pérez-García, Río-Valle, & Verdejo-García, 2010; Grant, Contoreggi, & London, 2000; Henry, Mazur, & Rendell, 2009; Henry, Phillips, et al., 2009; Leitz, Morgan, Bisby, Rendell, & Curran, 2009; Rendell, Mazur, & Henry, 2009; Terrett et al., 2014). For example, in studies by de Sola Llopis et al. (2008) and Fernandez-Serrano et al. (2010), individuals who used illicit substances performed significantly poorer across all tasks measuring executive functioning when compared to healthy, non-drug using individuals. In addition, drug users have been shown to exhibit significantly poorer decision making skills, verbal fluency and compromised inhibitory control (De Sola Llopis et al., 2008; Fernández-Serrano, Lozano, Pérez-García, & Verdejo-García, 2010; Fernández-Serrano et al., 2011; Fernández-Serrano, Pérez-García, et

al., 2010) than non-drug users; with more severe, chronic users showing more pronounced deficits in the above mentioned processes as well as in processing speed and memory functions (De Sola Llopis et al., 2008). Furthermore, evidence for the neurotoxic effects of illicit substances has emerged from studies identifying compromised neurocognitive processes in substance users even after the achievement of abstinence (Cheng et al., 2013; Henry, Mazur, et al., 2009; Rendell et al., 2009). Such deficits in higher-order cognitions have been used to explain impairments in social, financial, adaptive functioning (Goldstein, 1991; Goldstein & Volkow, 2002; Henry, Mazur, et al., 2009; Volkow, Fowler, Wang, & Goldstein, 2002) which are characteristic of individuals who engage in chronic substance use (American Psychiatric Association, 2013). However a noticeable exclusion from the substance use literature is the assessment of the cognitive ability of episodic foresight.

1.3 Introduction to episodic foresight

The concept of mental time travel was proposed by Tulving who originally differentiated memories relating to general information from memories of personally relevant information; semantic and episodic memories respectively (Tulving, 2002). Tulving went on to suggest that it is the *episodic memory* system that allows humans to re-experience events of the past. Subsequently, memory research extended this idea by investigating the memory for future intentions; that is, remembering to perform a task at a later date. This ability was termed *prospective memory*. Episodic and prospective memory have been shown to have some overlap as remembering to complete a task at a later date not only requires the recall that a task requires completion, but also recall of the *exact* task (Rendell, Gray, Henry, & Tolan, 2007). Both prospective and episodic memory have gained a large amount of research attention, interest however within the last decade research interest has increased regarding the ability to *pre-experience* events intended for the future (Atance & O'Neill, 2005; Schacter &

Addis, 2007). This process has many labels, but for the purpose of this research, it is referred to as *episodic foresight*.

In 2007 the topic of episodic foresight was named one of the top 10 trending areas in cognitive neuroscience (Science, 2007). Episodic foresight refers to the ability to mentally time travel into the future and pre-experience an event (Addis, Wong, & Schacter, 2007). Not to be confused with the ability to acknowledge the existence of a future time period, the defining element of episodic foresight is the ability to imagine what the experience would be like for the individual in that future time period (Addis et al., 2007; Schacter, Addis, & Buckner, 2007). It has been described as one of the fundamental human characteristics that separate our species from others (Suddendorf & Corballis, 2007). The adaptive value of episodic foresight has been highlighted throughout the literature and arguments against its importance are scarce (Suddendorf & Corballis, 2007). The current literature has not only identified the importance of this ability in day to day functioning (D'Argembeau, Renaud, & Van der Linden, 2011), but has also highlighted how impairments can significantly influence the adaptive functioning of vulnerable clinical groups (Brown et al., 2014; D'Argembeau, Raffard, & van der Linden, 2008; de Vito et al., 2012; Lind & Bowler, 2010; MacLeod, 2010; Raffard, D'Argembeau, Bayyard, Boulenger, & van der Linden, 2010; Sarkohi, Bjärehed, & Andersson, 2011; Terrett et al., 2013). With greater knowledge of this ability, including a better understanding of the cognitive processes that underpin it, a more holistic understanding of clinical presentations and their treatment responses can be developed; and if needed can inform alternative methods of therapeutic intervention.

1.4 Summary of the studies in the current research project

The overall objective of this research project was to investigate the cognitive ability of episodic foresight in users of illicit substances. This research project consists of three separate studies, reported in three individual journal articles, which address specific

objectives. The first of the three articles has been accepted for publication, and the two articles that follow have been submitted for review.

The first study was designed to address an identified gap in the understanding of episodic foresight ability among substance users. More specifically, given the well-documented neurological and functional consequences of chronic drug use, the first study assessed a sample of dependent drug users engaging in opiate substitution treatment. A number of impairments in future-oriented cognitions such as prospective memory (Terrett et al., 2014) and decision making (Brand, Roth-Bauer, Driessen, & Markowitsch, 2008; Piratsu et al., 2005; Rogers et al., 1999), have been identified in the context of chronic opiate use raising the possibility that impairment in the capacity for episodic foresight might also be apparent in this group. Furthermore, memory and executive control processes, which have been implicated in episodic foresight, are also compromised in long-term drug users. Therefore using a quasi-experimental design, the specific objectives of the first study of this project were:

1. To investigate episodic foresight ability in a group of long term opiate users
2. To determine whether memory and executive functions contribute to episodic foresight ability in the context of chronic, illicit substance use

The results of the first study identified specific episodic foresight impairment in the sample of long-term substance users. This deficit was not secondary to memory or executive control processing which raised questions surrounding what other abilities may be contributing to this identified impairment in episodic foresight. Recent literature has begun to explore the involvement of other cognitive abilities, such as scene construction and self-projection, in episodic foresight. As a result, the primary objective of the second study was:

3. To explore whether the identified episodic foresight deficit found in Study 1 may be attributable to compromised scene construction and/or self-projection

The findings of Study 2 identified a specific difficulty for opiate users in the capacity for self-projection into the future. The compromised episodic foresight as a result of impaired self-projection was discussed as a possible mechanism underpinning poor adaptive functioning and treatment success which are characteristic of this group.

However, considering that opiate use is relatively low in prevalence, the third study aimed to assess whether a similar deficit in episodic foresight would be observed in substance users of more commonly used substances, particularly cannabis. The third study employed the same methodology as Study 1 and assessed a group of recreational cannabis users on their episodic foresight ability. Thus the objectives of the third, and final, study of this project were:

4. To assess how episodic foresight is affected in the context of regular cannabis use
5. To examine the degree to which performance on measures of episodic foresight is correlated with performance on measures of episodic memory and executive control.

The results indicated an absence of episodic foresight, episodic memory, or executive function impairment in the context of regular cannabis use. These findings highlight that the capacity for episodic foresight is impacted differently within the context of different pharmacological substances. The results obtained from the three separate studies provide greater insight into the episodic foresight ability of different substance-using groups, which can have implications within therapeutic environments.

1.5 Outline of the thesis

This thesis begins with an introductory chapter followed by two separate literature review chapters providing research findings relevant to each of the three studies. The first review chapter presents the current literature regarding cognitive processing in the context of illicit substance use. The purpose of this review is to support the rationale for investigating the specific capacity of episodic foresight, which has been a notable exclusion from the current literature on substance use.

The second review chapter presents a review of episodic foresight literature. This chapter provides a definition and discussion of neurological underpinnings, contributing processes, functional importance, and evidence of episodic foresight deficits in other clinical populations. This chapter review sets the scene for all three empirical studies presented in this research project.

Each of the three journal articles, which are then presented, is preceded by a brief introduction chapter that reminds the reader of the relevant research literature used to develop each study's rationale. These chapters also outline the key findings and conclusions associated with each study.

This thesis concludes with an overall review and discussion chapter. This final chapter reviews the findings, limitations and conclusions of each study and discusses the functional implications and future research directions. The ethics approval letter from the Australian Catholic University Ethics Board that covers all three studies is included in Appendix A.

CHAPTER 2: Review of neurocognitive functioning within the context of substance use

Psychoactive substances exert their influence via altering neurocognitive processing (Goldstein, 1991; Koob & Volkow, 2010) either by mimicking naturally occurring neurotransmitters or by manipulating the release or recycling of these chemicals. Both lead to abnormal communication between neurons responsible for many aspects of emotional, cognitive, and behavioural functioning. This research project focuses on opiates and cannabis. Opiates (e.g. morphine, heroin) and cannabis represent substances commonly considered to lie at opposite poles of the drug-using spectrum. The former is considered a substance of choice for seasoned drug users, whereas the latter is generally associated with early experimentation. Each will now be considered in detail in terms of their respective neurological influence and associated cognitive dysfunction.

2.1 Opiates defined

Globally, opiate use accounts for the most drug-related diseases and deaths (United Nations Office of Drugs and Crime, 2014). Opiates have the capacity to cross the blood-brain barrier making them very potent substances (Denier, Schmidt, et al., 2013; Fu et al., 2008; Pau, Lee, & Chan, 2002). Route of administration is generally determined by the purity of the substance, but common methods include inhalation through nasal cavities (snorted), smoking, or intravenous injection; all of which lead to rapid delivery into the central nervous system (CNS). Opiates exert their influence by selectively binding to and activating opioid receptors found within various areas of the CNS including the amygdala, hypothalamus, cerebellum, brain stem, and spinal cord (Leri, Bruneau, & Stewart, 2003; Younger et al., 2011). Delta (Δ), kappa (κ), and mu (μ) receptors are the three different classes of opioid receptors that can be activated by both endogenous neuropeptides (e.g. endorphins) as well as exogenous compounds (e.g. morphine and heroin) (Leri et al., 2003; Waldhoer, Barlett, & Whistler,

2004). Opioid drugs are therefore categorized based on the type of receptor they bind to, with commonly abused drugs such as morphine and heroin primarily agonizing with μ - opioid receptors (Leri et al., 2003) which are particularly abundant in the amygdala and hypothalamus (key regions of the limbic system associated with reward, emotional regulation, and cognition). Given that opiates target key structures within the CNS, it might therefore be anticipated that neurocognitive impairment would be apparent.

2.2 Brain abnormalities associated with chronic opiate use

2.2.1 Structural changes

A number of different structural abnormalities have been reported within the context of chronic opiate use, including reduced ventricle/brain ratio (Wolf & Mikhael, 1979), volume loss in frontal regions (Pezawas et al., 1998), white matter abnormalities (Lyoo et al., 2004), reduced cerebral blood flow (Denier, Gerber, et al., 2013; Denier, Schmidt, et al., 2013), and decreased cortical thickness (Li et al., 2014). Although there is some variability in these findings likely reflecting differences in methodology and the heterogeneous substances use history common among life-long users of opiates, one structural change that has been repeatedly observed in the context of chronic opiate use is abnormal grey matter densities within key CNS regions (Denier, Schmidt, et al., 2013; Liu, Hao, et al., 2009; Lyoo et al., 2006; Qiu et al., 2013; Yuan et al., 2010; Yuan et al., 2009).

Grey matter refers to the neural tissue made up of cell bodies and glial cells. Given its composition, grey matter plays a fundamental role in receiving and transporting sensory information throughout the CNS and the body. The brain is predominately made up of grey matter and areas of high density tend to be associated with high levels of functioning related to the specific brain region. Therefore reductions in grey matter would be expected to be reflected in impaired cognitive ability.

In one study addressing this question in the context of substance use, Lyoo et al. (2006) compared the grey matter density of a large group of opiate-dependent individuals ($n = 63$) with a matched group healthy controls. The authors were the first to use Voxel-based morphometry (VBM) to assess grey matter concentrations within the brains of opiate-dependent individuals (see Ashburner & Friston, 2000 for detailed description of VBM). The images identified that relative to the healthy comparison group, opiate-dependent participants had reduced grey matter concentrations within prefrontal and temporal cortices. Similarly, Yuan et al. (2009) observed reduced concentrations of grey matter within the prefrontal, temporal, as well as the anterior cingulate, and insular cortices. Both studies suggested that these findings might provide some explanation for compromised processing in executive, sensory, memory, and emotional domains that are governed by these regions. Interestingly, Yuan et al. (2009) also observed a correlation between duration of opiate use and grey matter density (longer opiate use was associated with lower the grey matter concentrations). Interestingly, unlike most studies of opiate dependence, the sample recruited by Yuan et al. (2009) could be considered a novice group of opiate users (mean age = 23.97 years, mean duration of use = 4.93 year) therefore the relationship found in that study between duration of use and grey matter concentrations highlights a detrimental effect of opiate use on neurocognitive functioning, even within the early years of use. Thus, although structural imaging studies relating to chronic opiate use are limited, those that have been conducted have consistently demonstrated that relative to healthy individuals, long term opiate users have significant reductions in grey matter density within prefrontal and temporal brain regions, which are areas responsible for a number of important processes such as executive and memory functions, respectively.

2.2.2 Functional resting-state abnormalities

There has however been some criticism of previous structural imaging studies with Yuan et al. (2010) arguing that they have limited clinical significance given that structural and functional abnormalities within the context of opiate use tend to be examined in isolation. As a result, they conducted a study of grey matter deficits associated with opiate use that focused on an association between structural irregularities and functional connectivity during resting-state. *Resting-state* functional connectivity refers to the activity of neural circuits of the resting-brain and is assessed using functional magnetic resonance imaging (fMRI) which allows for the examination of unaltered inter-region connectivity. Observation of abnormalities in connectivity during resting-state can predict alterations of neurocognitive activation of the same brain areas during performance of domain specific tasks (Sutherland, McHugh, Pariyadath, & Stein, 2012). Abnormal resting-state functional connectivity between key CNS brain regions in long-term opiate users has been observed in a number of studies (Cheng et al., 2013; Liu, Liang, et al., 2009; Ma et al., 2010; Yuan et al., 2010).

The initial findings of Yuan et al. (2010) were consistent with the literature as they found reduced grey matter concentrations in frontal, (right dorsolateral pre-frontal cortex (DLPFC)) and temporal regions (right fusiform gyrus and left middle cingulate cortex), as well as in the left parietal lobe. However as noted, the novel element of this study was the examination of the relationship between these anatomical deficits and resting-state functional connectivity, and also whether the connectivity between brain regions during resting-state was associated with duration of opiate use. The authors did indeed observe reduced connectivity between the right DLPFC and the inferior parietal lobe in the opiate group highlighting an association between structural changes and functional connectivity in these areas. These findings suggest that processes governed by the DLPFC and the inferior parietal lobe, such as decision-making and working memory respectively, may be particularly

vulnerable to impairment within the context of opiate use. In addition, the authors also observed a negative relationship between the duration of opiate use and the functional connectivity between these two areas, highlighting that the cumulative negative effect of opiates not only applies to neurological structures (as discussed earlier), but also extends to functional connectivity.

Others investigations that identified dysfunctional resting-state connectivity between key CNS brain regions in opiate users include a study by Liu, Liang, et al. (2009) which identified abnormalities in the pre-frontal cortex (PFC), anterior cingulate cortex (ACC), supramarginal motor area, ventral striatum, hippocampus, amygdala, and insula. In addition, Ma et al. (2010) observed increased connectivity between the nucleus accumbens and ACC, and orbito frontal cortex (OFC), and between the amygdala and OFC; but reductions in connectivity were observed between the pre-frontal cortex (PFC) and the anterior cingulate cortex (ACC) in long term opiate users. Cheng et al. (2013) also reported irregular connectivity between the right DLPFC and each of the following brain regions: the OFC, right entorhinal cortex (EC; part of the medial temporal lobe [MTL]), occipitoparietal cortex (OC) and ACC.

Despite the methodological variations between the studies, the findings all highlight significant abnormalities within key CNS regions both in terms of decreased grey matter concentrations as well as dysfunctional connectivity at resting-state. The cognitive domains underpinned by these regions include inhibitory control (PFC, ACC), conflict monitoring (ACC), reward processing (nucleus accumbens), motivation (OFC), learning (amygdala), and memory (hippocampus) (Baler & Volkow, 2006). Therefore disruption to circuitry between these regions is likely to lead to a breakdown in these cognitive faculties.

2.2.3 Effects of opiates on immunology

Cheng et al. (2013) also examined the relationship between structural and functional processing associated with opiate use. However, rather than focusing on grey matter concentrations the authors were the first to investigate cell immunology in the context of long-term opiate use by examining telomerase. Telomerase refers to an enzyme that prevents the shortening of chromatin structures known as telomeres which are found at the end of chromosomes. In essence, telomerase prevents cellular aging (Campisi & d'Adda di Fagagna, 2007) therefore declines in telomerase activity indicate acceleration of aging. Research has indeed identified age-related declines in telomerase activity (Blasco, 2005). Cheng et al. (2013) observed reduced telomerase activity within the right DLPFC of opiate users, relative to a healthy control group. Given that the prefrontal structures are particularly vulnerable to the aging process (Burke & Barnes, 2006; Reuter-Lorenz & Lustig, 2005) this observation prompted Cheng et al. (2013) to conclude that chronic opiate use accelerates the aging process (at least on a cellular level). Also, because both healthy aging and opiate using groups have demonstrated similar atrophy in the DLPFC, it has been postulated that similar age-related cognitive declines would be expected within the context of chronic opiate use, which may assist in explaining deficits in cognitive functioning commonly associated with this group.

Overall, the cumulative neuroimaging evidence relating to chronic opiate use suggests that a number of cognitive domains are vulnerable to impairments. In particular, given that prefrontal regions govern higher-order cognitions known as executive functions and the temporal areas of the brain are implicated in memory-related processes, it might be anticipated that these processes would be vulnerable.

2.2.4 Opiate-related declines in executive functions

Executive functions refer to complex goal directed cognitive faculties including inhibitory control, attention, decision-making, memory, and planning. Given the prominence of these abilities in everyday life, dysfunction within any of these domains can create significant difficulty in the fulfilment of even basic responsibilities, let alone more demanding obligations. Executive dysfunction has been linked to atrophy within frontal brain regions, and groups with established frontal lobe damage (e.g. Parkinson's disease, Alzheimer's disease) have been shown to display deficits in higher-order cognitions (de Vito et al., 2012; Irish & Piguet, 2013). Given that opiates have the capacity to impact structural features and functional processing in frontal brain regions it might therefore be expected that these higher-order cognitions would also be substantially impaired.

A number of studies have identified significant impairments in executive processes within the context of chronic opiate use in comparison to healthy control groups. For example, Pau et al. (2002) examined the impact of opiate use on performance across a number of neuropsychological measures. The authors compared a group of opiate addicted individuals with a healthy comparison group. The findings indicated that chronic opiate use was associated with compromised impulse control; a result that was also found in subsequent studies (Brand et al., 2008; Posser et al., 2006). Other compromised executive processes that have been reported include attention (Brand et al., 2008; Darke, Sims, McDonald, & Wickes, 2000) cognitive flexibility (Brand et al., 2008), cognitive initiation/verbal fluency (Davis, Liddiard, & McMillan, 2002), and decision making (Brand et al., 2008; Ersche, Clark, London, Robbins, & Sahakian, 2006; Fishbein et al., 2007), all of which are imperative for successful day-to-day living. However, while these studies suggest that executive control impairment is associated with chronic opiate use, the picture is not clear-cut. In fact, some studies of this group have reported minimal (Pau et al., 2002) or no impairment (Terrett et al.,

2014) in higher-order cognitions. These inconsistencies may reflect methodological differences (e.g. in terms of choices of measurement) and also the heterogeneous nature of this population.

2.2.5 Opiate-related memory declines

There are a number of different types of memory processes, including episodic memory, working memory, and prospective memory. Episodic memory refers to the capacity to retrieve and mentally reconstruct personally experienced events whereas working memory refers to the memory store which allows for the temporary storage and subsequent manipulation of newly learnt information (Tulving, 1985). Prospective memory on the other hand refers to the ability to remember to complete future intentions (Einstein et al., 2005). The different forms of memory are associated with different temporal regions (e.g. hippocampus, basal ganglia) but the execution of these memory functions is complex and can incorporate different neural networks (Moscovitch, 1992).

These memory processes play an important role in every day functioning. For instance, when making choices for future actions we usually draw upon our experiences from the past (i.e. episodic memory) to inform those decisions. Those actions that resulted in unrewarding outcomes in the past would therefore be altered in order to increase the likelihood of improved results and future goal attainment. Impairments in prospective memory also have the potential to significantly affect the execution of everyday tasks and the maintenance of social engagement, and threaten treatment compliance as this cognitive faculty supports the ability to not only remember that a future task needs executing, but also what that task is. As previously mentioned, given the identified atrophy within temporal regions associated with chronic opiate use, impairment in these memory processes would therefore be expected. This has been shown in empirical studies which have identified opiate-specific deficits in various memory functions including episodic memory, working memory,

and prospective memory (Curran, Kleckham, Bearn, Strang, & Wanigaratne, 2001; Darke et al., 2000; Ornstein et al., 2000; Terrett et al., 2014). However similar to the literature surrounding opiate use and executive functioning, the findings for opiate-related memory impairments are not consistent (e.g. Fernández-Serrano, Pérez-García, et al., 2010; Fishbein et al., 2007). Reasons for this include methodological differences relating to neuropsychological battery chosen, the heterogeneous nature of substance use histories reported by chronic opiate users, onset and duration of opiate use, and rates of concurrent poly-substance use tend to be high in this drug using group, making it extremely difficult to recruit pure opiate users and delineate the effects of other substances.

2.3 Cannabis

Another psychoactive substance that has been the subject of increasing research interest within the cognitive neurosciences is cannabis. Although it is generally considered a benign substance, cannabis continues to be the world's most used illicit drug with at least 180 million users globally, and cannabis dependence is the most common type of substance addiction (after alcohol and tobacco) in a number of developed countries including the United States, Canada and Australia (United Nations Office of Drugs and Crime, 2014). Furthermore, there has been a recent increase in cannabis related treatment enrolment with a 59% rise in cannabis-related emergency visits between 2006 and 2010 in the United States alone (United Nations Office of Drugs and Crime, 2014) challenging the notion that it is a substance devoid of negative outcomes. Initial use tends to occur during late adolescence and this early introduction to the drug can significantly alter neuronal development (Parker, Williams, & Aldridge, 2002) and increases the likelihood of developing future addiction by six fold (Wagner & Anthony, 2002).

2.4 Cannabis defined

Cannabis is derived from the *Cannabis sativa* plant which contains over 70 unique chemical compounds known as cannabinoids (Pertwee, 2008). The highest concentrations of cannabinoids are found in the flowering tops of the plant whereas very small densities are found in the stem and roots (Ameri, 1999). The primary cannabinoid responsible for the desired psychoactive effects of cannabis is Δ^9 – tetrahydrocannabinol (THC) which binds to the CB1 – cannabinoid receptors found within the endocannabinoid neural network (Batalla et al., 2013). Like most psychoactive substances, THC exerts its influence by activating the release of dopamine, a neurotransmitter largely implicated in the pleasure and reward systems. Brain regions with high densities of cannabinoid receptors include the prefrontal cortex, cerebellum, striatum, amygdala, and hippocampus (Ameri, 1999; Glass, Dragunow, & Faull, 1997; Mechoulam & Parker, 2013; Quickfall & Crockford, 2006) therefore any negative impact of cannabis use might be anticipated to be particularly apparent in these regions.

2.5 Brain abnormalities associated with cannabis use

2.5.1 Structural atrophy

According to Yücel et al. (2008) animal studies provide the strongest argument for the notion that cannabis is neurotoxic for the brain. For instance, an early rodent study by Landfield, Cadwallader, and Vinsant (1988) identified hippocampal changes in response to long-term THC exposure. The investigators observed decreased neuronal densities within this region and concluded that their observations provided evidence that chronic exposure can lead to structural changes in the brain. Chan, Hinds, Impey, and Storm (1998) observed THC-related neuronal death within hippocampal slices of rodent brains and Lawson, Borella, Robinson, and Whitaker-Azmitia (2000) identified morphological changes in the

hippocampus of male rodents which were reminiscent of alterations seen as a result of ischemic or traumatic brain injury. The authors of these studies postulated that the THC-related structural changes observed in rodent brains might be paralleled in the brains of cannabis users and in turn may help explain, at least to some extent, the cognitive difficulties often reported and observed in users of the drug. However, similar to the opiate-related literature, investigations of cannabis use in humans have produced a heterogeneous literature regarding cannabis-related structural and functional brain changes.

For example, Matochik, Elderth, Cadet, and Bolla (2005) observed differences in both grey and white matter densities between heavy cannabis users and non-using individuals. More specifically, the investigators identified reductions in grey matter concentrations within hippocampal regions but increased white matter densities within temporal lobe areas (fusiform gyrus and parahippocampal gyrus), the lentiform nucleus and in the pons of the brainstem. Furthermore, a study by Yücel et al. (2008) reported that chronic and heavy cannabis use was associated with volumetric reductions of the hippocampus and amygdala. They went on to further conclude that the decrease in hippocampal volume was a function of cumulative cannabis exposure, and although they did not anticipate the reduction in size of the amygdala it is not a surprising outcome given that this area is also richly dense in cannabinoid receptors (Ameri, 1999; Quickfall & Crockford, 2006).

A similar reduction in hippocampal volume has also been observed in adolescents with a history of heavy cannabis use (Ashtari et al., 2011). The cannabis-using group reported at least one year of heavy cannabis consumption (average daily use reported as 5.8 joints), but were currently abstinent (average length 6.7 months) and seeking treatment. In the cannabis group both the left and right hippocampi were significantly lower in volume (14.2% and 12.6% reductions respectively) than the healthy, non-using control group. This reduction in structural volume was also negatively correlated with amount of cannabis use. That is, the

higher the cannabis consumption, the smaller the hippocampal volume observed. This study not only identified cannabis-related structural changes, but also indicated that early and heavy cannabis use can result in persistent neurological impairment.

Zalesky et al. (2012) used axonal connectivity as a means to assess whether long-term cannabis use was associated with microstructural white matter alterations. The investigators observed impaired axonal connectivity within the hippocampus of their cannabis-using sample, relative to a healthy comparison group. The investigators also identified that the age of onset of cannabis use was positively related to the severity of the white matter alterations, leading to the conclusion that the early introduction to cannabis use can increase the level of neurological impairment. This finding is consistent with that of Churchwell, Lopez-Larson, and Yurgelun-Todd (2010) who reported that reductions in neuronal tissue volumes within the medial prefrontal cortex were associated with age of first use, therefore suggesting that early initiation into cannabis use may lead to greater structural atrophy.

In a very recent investigation, Battistella et al. (2014) observed reduced grey matter volume in a number of brain areas of cannabis users including hippocampal regions. Reductions were observed in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex (OFC). These reductions were strongly associated with frequency of use indicating that increased use may intensify the severity of cannabis-related neurological atrophy. Similar to previous studies (Churchwell et al., 2010; Zalesky et al., 2012), age of onset was suggested to be a factor contributing to grey matter reductions, with younger (during adolescence) initiation to recreational cannabis use potentially playing a crucial role in the reduced grey matter concentrations. However, it was also proposed that heavy use of cannabis irrespective of age of onset contributed to the neuronal tissue decrease. It should be noted however that not all studies of cannabis users have reported structural brain abnormalities. For example, Block, O'Leary, Ehrhardt, et al. (2000) did not observe any

cannabis-related changes in global or tissue volume when they assessed a group of frequent cannabis users and compared them to non-using controls. Similarly, Tzilos et al. (2005) failed to identify abnormalities in neuronal tissue or hippocampal volume in long-term cannabis users. Explanations for these inconsistent findings have focused on variations in aspects of methodology (e.g. sample size, brain scanning method) and participant characteristics, such as differences in substance-using histories.

2.5.2 Functional resting-state abnormalities

Over and above structural abnormalities, global and regional resting-state brain abnormalities have also been observed in frequent cannabis users. For example, Block, O'Leary, Hichwa, et al. (2000) compared the regional brain blood flow of frequent cannabis users to a group of non-using controls. The cannabis group recruited for this study were regular users of the drug with the average frequency of use reported as at least seven times per week. The group did not have any past or current substance dependence, and were assessed after at least 26 hours of hospital monitored abstinence to control for potential effects of short-term withdrawal. Results of positron emission tomography (PET) imaging data revealed region specific functional abnormalities within the posterior cerebellum of the cannabis group. Given that the cerebellum is implicated in the internal timing system, it was concluded that the hypoactivity observed in this region during resting-state may contribute to the altered time perception commonly experienced during cannabis intoxication.

In addition, Lundqvist, Jönsson, and Warkentin (2001) assessed the cerebral blood flow of a group of cannabis dependent users ($n = 12$) and an aged matched group of healthy control participants. The cannabis group were assessed within five days of voluntary cessation from their regular use. The findings highlighted decreased hemispheric blood flow for both cerebral hemispheres within the cannabis group, as well as regional reductions within prefrontal, superiorfrontal, and central areas. Reductions in cerebral blood flow to

frontal regions could pose a significant threat to cognitions governed by these areas. For instance, it is well documented that executive functions (e.g. decision making, planning, and cognitive flexibility) are particularly sensitive to prefrontal dysfunction (Dubois, Slachevsky, Litvan, & Pillon, 2000). Therefore significant cannabis-related reductions in cerebral blood flow could lead to tissue death which can potentially give rise to a break down in cognitive processing.

Sevy et al. (2008) used PET to measure dopamine receptor availability and cerebral glucose metabolism in a small group ($n = 6$) of young adults (18 – 21 years old) diagnosed with cannabis dependence in full remission. Although the investigators did not find any difference in the dopamine receptor density, they did observe reduced glucose metabolism in the right OFC, putamen bilaterally, and precuneus. This finding provides more support for the notion of cannabis-related neurological harm. The metabolism of glucose is imperative for brain functioning (Mergenthaler, Lindauer, Dienel, & Meisel, 2013). Neurons are one of the cell types that particularly rely on glucose for energy therefore disruptions to the metabolic breakdown of glucose can pose significant threat to cell functioning in areas responsible for cognitive processing (Mergenthaler et al., 2013).

Orr and colleagues (2013) also assessed neurological functioning in the context of chronic cannabis use, but in a sample of cannabis-dependent adolescents ($n = 17$). Their findings further highlighted cannabis-related changes in neurological functioning. Relative to healthy control participants, the cannabis-using adolescents displayed significant neurological abnormalities which may have the potential to alter the execution of cognitive tasks. The primary findings illustrated that the functional connectivity between the fronto-parietal and cerebellar regions was greater for the cannabis-dependent group particularly in the right hemisphere. The authors suggested that the increase in functional connectivity may be indicative of compensatory mechanisms. That is, in the context of chronic cannabis use, more

effort is required in order to execute cognitive tasks. Orr et al. (2014) also identified a reduction in homotopic connectivity (inter-hemispheric communication) of cerebellar and fronto-parietal regions, possibly reflecting the negative impact of chronic cannabis use on the integrity of the corpus callosum. This outcome is particularly important because inter-hemispheric communication is necessary for coherent cognition and behavioural performance. Disruptions in functional connectivity between hemispheres have been identified in psychiatric disorders that are characterised by significant cognitive and behavioural difficulties (e.g. schizophrenia, autism, attention deficit hyperactivity disorder) (Clarke et al., 2008; Pettigrew & Miller, 1998; Spencer et al., 2003). Therefore the reduction in inter-hemispheric communication may potentially play a significant role in the level of functioning displayed by chronic cannabis users.

More recently, Fibely et al. (2014) identified significant changes in the OFC in a sample of long-term adult cannabis users ($n = 48$). This sample included a subset ($n = 25$) of cannabis-dependent individuals. In comparison to a group of non-using control participants, the chronic users had lower grey matter volumes within the OFC, and this finding remained in the smaller sample of dependent users. The authors described this finding as unsurprising given that the OFC is highly dense in CB1 receptors, and is a significant region with the reward network; an area implicated in the development and maintenance of addiction. A secondary finding from this study was the increased functional connectivity between the OFC and other brain regions. Similar to Orr et al. (2013) the authors suggested that the contrast between these two main findings may indicate neurological compensation. The down-regulation within the OFC supports claims about the neurotoxicity of cannabis, but the increased connectivity within the OFC network may be indicative of the need for greater processing in order to execute various cognitive tasks.

Pujol et al. (2014) explored functional resting-state connectivity in a group of cannabis-dependent adult male ($n = 28$). The authors focused on the Default and Insula networks, areas associated with self-awareness. It is widely accepted that these two networks make different contributions to the capacity for self-awareness. The primary elements of the Default network are the posterior cingulate cortex (PCC) and adjacent precuneus, angular gyri and medial frontal cortex. Functions include supporting the ability to recognise the body and its interaction with the external environment, solving moral dilemmas, assisting in the comprehension of another individual's perspective, retrieving autobiographical memories, and prospective thinking. The Insula network however contributes to the capacity for introspective awareness, including conscious awareness of physiological conditions and emotional experiences. These two networks do not function in isolation but share relevant overlap. In the context of chronic cannabis use, Pujol and colleagues identified various alterations in functional connectivity within these two brain networks. In relation to the Default network, increases and decreases in functional connectivity were identified in the PCC and these alterations in connectivity were linked to reduced memory abilities. Increased functional connectivity was found in the Insula network and it was suggested by the authors that the activation of this network may play a role in the modification of an individual's subjective affective state. The intricacies of the neurological alterations identified in the aforementioned studies are beyond the scope of this research project. However, these studies highlight that cannabis-use has the potential to significantly alter resting-state functioning and therefore suggests that alterations may also be found in cognitive functioning.

2.5.3 Cannabis-related cognitive impairments

Although there is continued debate over the impact of cannabis consumption on cognitive functioning, a number of studies have highlighted the potential for compromised abilities in this domain. For example, Bolla, Elderth, Matochik, and Cadet (2005) assessed a

group of abstinent cannabis users (at least 25 days of abstinence following an average of 5 years heavy use) on their decisional making capacity using the Iowa Gambling Task. Relative to a matched control group, the cannabis group demonstrated poorer performance on the task, indicating hypersensitivity to immediate rewards but not to potential losses or negative outcomes. In another study Abdullaev, Posner, Nunnally, and Dishion (2010) reported that chronic cannabis use during adolescence contributed to a compromised attention network, particularly related to conflict resolution. The cannabis group took more time to resolve presenting conflicts and were more erroneous in their choices, relative to the control group. Previous studies also observed compromised response monitoring ability within samples of cannabis users reflected in their reduced capacity to recognise errors in performance (Gruber & Yurgelun-Todd, 2005; Hester, Nestor, & Garavan, 2009). However the studies conducted by Gruber and Yurgelun-Todd (2005) and Hester et al. (2009) did not identify overarching deficits in cognitive domains. For example, the cannabis group in these studies performed comparably to the controls on measures of inhibitory control (the Stroop and Go/No-go response tasks, respectively).

Given the high cannabinoid concentrations within the hippocampus and surrounding regions, the literature tends to focus on investigating possible cannabis related impairments in functions associated with these areas. One of the most frequently investigated domains is memory. A number of recent reviews on the neuropsychological impact of cannabis use have repeatedly highlighted consistent findings within the literature associating cannabis use with compromised memory abilities (Gonzalez, 2007; Hall, 2014; Solowij & Battisti, 2008). For example, in a study involving a particularly large sample size than is usual in studies of cannabis users ($n = 51$) Solowij and Battisti (2008) compared the performance of long-term, heavy cannabis users to a sample of shorter-term users ($n = 51$) and a control group. The heavy users were significantly poorer in the execution of memory and attention based tasks

compared to the shorter-term using group and the control participants, and no differences were found between the latter two groups. Of all the measures administered, the greatest difference in performance was observed in the memory assessment (RAVLT), indicating a global impairment in learning, retention and retrieval of information. The authors concluded that heavy cannabis use is associated with impairments that persist beyond intoxication and furthermore that cannabis-related declines were a function of the duration of use.

The literature tends to conclude that the level of decline in cognitive processing as a result of cannabis use is influenced by a number of factors including dose, type of cannabis, frequency, duration of use, and age of initial onset (Bolla et al., 2005; Curran, Brignell, Fletcher, Middleton, & Henry, 2002; Gonzalez, 2007; Hall, 2014; Morgan, Schafer, Freeman, & Curran, 2010; Solowij & Battisti, 2008). For instance, in a study of recreational cannabis users Curran et al. (2002) identified greater impairments in cognitive functioning in response to higher doses of orally administered THC, with impairments more evident two hours after consumption. Furthermore, Bolla et al. (2005) reported that cannabis-related impairments in decision-making were also related to frequency of use with greater deficits observed in more frequent users. Also, Morgan, Schafer, et al. (2010) observed no memory deficits in users who smoked cannabis with higher levels of cannabidiol (CBD; another primary component of cannabis) leading to the suggestion that high CBD strains could offset memory impairment associated with THC. Interestingly, a number of studies have reported an absence of cannabis-related cognitive impairment, despite the observation of altered neurological functioning (Chang, Yakupov, Cloak, & Ernst, 2006; Elderth, Matochik, Cadet, & Bolla, 2004; Filbely et al., 2014; Nestor, Hester, & Garavan, 2010; Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2010). Absences of cognitive impairments have been attributed to participant (e.g. substance use history) and methodological factors such as the choice of imaging methods (computed tomography, PET, fMRI) and use of a wide variety of different

neuropsychological tools. However some studies have proposed that the lack of differences in cognitive abilities in the presence of abnormal neural functioning may be the result of compensatory mechanisms whereby other brain regions are recruited to assist in the execution of cognitive processes (Chang et al., 2006; Elderth et al., 2004; Fibely et al., 2014; Nestor et al., 2010; Schweinsburg et al., 2010). Whatever the reason, it is nevertheless apparent that the literature relating to cannabis-specific cognitive declines is characterised by mixed findings across a range of cognitive processes.

2.6 The importance of investigating cognitive processing within substance-using samples

Given the heavy reliance we place on cognitive processes in order to function effectively in our daily lives and the fact that compromised cognitive functioning perpetuates compulsive drug using behaviour increasing the likelihood of addiction (Goldstein & Volkow, 2002; Koob & Volkow, 2010; Volkow & Fowler, 2000), it is clearly important to continue to investigate the cognitive profiles associated with substance use. Furthermore, the identification of drug specific declines across various stages of consumption could assist in the development of more tailored support strategies that take into account reduced cognitive abilities. By doing so, improvements in basic day-to-day functioning, as well as increases in treatment compliance and prognosis could be achieved.

2.7 Gaps in the literature regarding cognitive functioning in substance users

Although a number of cognitive processes have been investigated within the context of both opiate and cannabis use, there is one striking omission, namely the capacity to mentally time travel into one's personal future. This process has been referred to by a number of labels including future thinking, episodic future thinking, prospection, and episodic foresight (Addis et al., 2007; Atance & O'Neill, 2001; Buckner & Carroll, 2006; Schacter et al., 2007; Suddendorf & Corballis, 2007). For the purpose of this research project, it will be

referred to as episodic foresight. This particular capacity is considered by some to be a defining ability separating humans from less evolved species (Suddendorf & Corballis, 2007) and it has recently been the subject of increasing research interest. It shares neurological and cognitive overlap with memory and other higher-order processes (Addis, Musicaro, Pan, & Schacter, 2010; Addis & Schacter, 2008; D'Argembeau, Ortoleva, Jumentier, & Van der Linden, 2010; D'Argembeau, Xue, Lu, van der Linden, & Bechara, 2008; Schacter & Addis, 2007; Schacter et al., 2007) and therefore conditions which bring about impairments in these associated domains would likely also be associated with impaired episodic foresight. This research project, to our knowledge, is the first investigation of episodic foresight within the context of psychoactive substance use.

CHAPTER 3: Review of episodic foresight literature

3.1 Definition of mental time travel

The faculty of mental time travel (MTT) allows humans to reminisce about past experiences and entertain possibilities in their personal future (Suddendorf & Corballis, 2007; Tulving, 1985, 2002). This process requires disengagement from current experiences in order to re-live or pre-live events in the present moment. MTT is phenomenological in nature and has immense survival value as present behaviours are informed by the recollection of past experiences as well as anticipation of future outcomes. There is now recognition that MTT into both the past and future are complementary processes with converging lines of evidence consistently highlighting an association between the ability to recall the past (episodic memory) and pre-experience the future (episodic foresight).

3.2 Episodic memory and episodic foresight defined

Although the human memory system encompasses a catalogue of memory functions, it is the episodic memory system which is most implicated in MTT into the past and future (Busby & Suddendorf, 2005; Tulving, 1972, 1985, 2002). One part of this system is episodic memory which is distinguished from other types of memory by its temporal orientation and first-person perspective (Tulving, 2002). Unlike semantic memory, which refers to the factual knowledge related to the world and not personal experiences, episodic memories refer to autobiographically-referenced experiences which are specifically oriented to past (Tulving, 2002). Referring to the capacity to mentally project the self into the future and pre-experience an event, episodic foresight is a uniquely human ability (Addis, Wong, & Schacter, 2008; Atance & O'Neill, 2001; Schacter et al., 2007). Different from the acknowledgement of a future time period, episodic foresight involves *pre-living* the future through mental simulation. Given that future survival is a function of behaviours executed in the present,

episodic foresight has immense survival value as it allows for the construction, mental enactment, and evaluation of behavioural contingencies before committing to any course of action (Suddendorf & Corballis, 2007). This capacity to generate and work through multiple future scenarios allows for the expansion of viable possibilities as well as elimination of less appropriate alternatives. The mental simulation of these hypothetical outcomes provides a safe environment to test the practicality of options without the risk of harm or unnecessary use of physical resources. The autobiographical nature of this memory system is attributed to auto-noetic consciousness, which is the subjective sense of the self as it extends across time (Suddendorf & Corballis, 2007; Tulving, 1985, 2002). Without auto-noetic consciousness, humans are devoid of MTT ability into either the past or indeed the future (Tulving, 2002).

3.3 Importance of episodic foresight

The potential functional implications of impaired episodic foresight ability cannot be understated given its prominent role in basic day-to-day existence. D'Argembeau et al. (2011) highlighted the important role thinking about the future plays in the everyday lives of healthy adults, reporting that the frequency of future-oriented thoughts outweighs those about the past, with a future thought occurring every 16 minutes. In fact, individuals tend to simulate hypothetical future outcomes when engaging in processes central to basic daily functioning such as planning, decision making, and problem solving (D'Argembeau et al., 2011). However despite the many discussions proposing links between episodic foresight and mental processes implicated in functional outcomes (Atance & O'Neill, 2001; Buckner & Carroll, 2006; Busby & Suddendorf, 2005; D'Argembeau et al., 2010; Schacter et al., 2007; Suddendorf & Corballis, 2007), this area is lacking in direct empirical evidence. Of the studies that have been conducted linking functional capacities and episodic foresight specifically most tend to focus on how the mental simulation of future events can lead to successful goal attainment by increasing the likelihood of performing intended actions. For

example, in a study by Taylor, Pham, Rivkin, and Armor (1998), university students studying for an impending mid-term examination were trained to either mentally simulate scenarios of themselves studying in a way that could lead them to obtaining an A grade (process-simulation) or to imagine themselves receiving the A grade (outcome-simulation). Both groups were told to engage in these simulations each day in the week leading to the exam. The students who executed the process simulations reported more time studying for the exam and achieved higher grades on the actual mid-term, in comparison to a matched control group; whereas the outcome-simulation group did not benefit from their mental simulations. It was proposed that the benefits gained by using process-simulations were in part due to the mental simulations facilitating the students to plan for the exam. The rationale behind this is that mental simulations of scenarios that involve the execution of future intentions can assist in the translation of the intention into an actual behaviour (Gollwitzer, 1993; Gollwitzer & Sheeran, 2006; Neroni, Gamboz, & Brandimonte, 2013). Difficulties in the capacity for episodic foresight could potentially limit the frequency of behavioural contingencies constructed, restricting choice of actions that would potentially achieve desired goals.

3.4 The role of episodic memory in episodic foresight: the constructive episodic simulation hypothesis

Recalling the past and imagining the future are both constructive processes requiring the assembly of mental scenes. According to the *constructive episodic simulation hypothesis* episodic foresight involves two main processes, the first of which is a construction phase (Addis et al., 2007). In this phase, the simulation of personally relevant future events relies heavily on the retrieval of autobiographical memories from the past in order to provide the basic building blocks for the construction of novel future scenarios (Schacter et al., 2007). The second phase involves inhibiting the tendency to simply recast actual memories and requires that the retrieved information be held in mind and flexibly manipulated so that past

details are recombined into novel future scenarios (Schacter & Addis, 2007). Referred to as the elaboration phase (Addis et al., 2007), this secondary process of recombining past information into a novel future experience is critical as it allows for the simulation of alternative scenarios without the need for behavioural engagement (Schacter & Addis, 2009). The constructive episodic simulation hypothesis was further extended to offer an explanation for why the reconstructive nature of episodic memory allows for future event simulation (Schacter & Addis, 2007). Specifically, because the recall of past memories is a reconstructive process, experiences of past events are not retrieved from memory stores as a whole, but rather as pieces of information. When cued, both internally or externally, these pieces of information are searched for within memory traces and the whole experience is reconstructed from these parts. Therefore, episodic memory assists in episodic foresight by making these pieces of information available for assimilation into a novel future scenario. There is a considerable body of research confirming the overlap between past and future MTT.

3.5 Assessment of episodic foresight

Research studies often employ the use of interview tasks to assess episodic foresight ability. These commonly involve word-cue techniques in which participants are instructed to mentally simulate and describe events personally experienced in the past and imagine plausible future events that could occur in their personal future (Atance & O'Neill, 2005; Busby & Suddendorf, 2005; Hassabis, Kumaran, Vaan, & Maguire, 2007). A widely used example of this approach to episodic foresight assessment is the adaptation by Addis et al. (2008) of Levine, Svoboda, Hay, Wincour, and Moscovitch's (2002) Autobiographical Interview (AI). The adapted AI is a semi-structured interview used to assess episodic and non-episodic content in two temporal phase conditions (past and future) and therefore provides an index of both episodic memory and episodic foresight. Participants are instructed

to describe a previously-experienced past event or a novel future event in response to a cue word. The events have to refer to a specific time and place, and be described from the participant's subjective perspective, rather than that of an observer. In the Addis et al. (2008) version of the measure, 32 cue words are provided across four temporal conditions (past few weeks, past few years, next few weeks, and next few years) and participants are given a limit of three minutes to describe each event. Performance on this task is assessed by segmenting and categorizing the details generated from the interview as either internal (episodic details specific to the central event) or external (non-episodic details including: repetitions, semantic information, and information not specific to the central event). The number of internal details generated for future events is the primary measure of episodic future thinking and the number of internal details for past events indexes episodic memory.

3.6 Evidence for episodic memory and episodic foresight overlap

3.6.1 Developmental evidence

If there is an overlap between episodic memory and episodic foresight, both abilities should begin to emerge and decline in tandem across the life span. In relation to episodic memory there is a large body of literature that consistently demonstrates that it is not fully developed until a child reaches the age of four (see Atance & Metcalf, 2013 for review). This is not to suggest however, that children younger than four years of age have no memory of the past. Instead it is suggested that younger aged children have script-like or semantic based knowledge of past experiences rather than memories that are truly self-relevant, reflecting a lack of autonoetic consciousness.

The developmental trajectory of episodic foresight has been shown to parallel the emergence and decline of episodic memory. For example, Busby and Suddendorf (2005) observed similar difficulty in future-oriented thinking when asking three -, four -, and five-year old children about events they experienced "yesterday", as well as experiences they

might have “tomorrow”. Only a small minority of three year-old children were able to successfully provide accurate reports of events they experienced the day prior to testing, or would experience the following day. The four and five year-old children performed better than the three year-olds on both tasks but there were no differences observed between the four year old and five-year olds. Although tentatively proposed, these findings could suggest that the capacity for MTT into the past and the future is not yet fully developed in three-year children (Busby & Suddendorf, 2005).

At the other end of the life span, research has identified comparable age-related declines in episodic memory and episodic foresight. For example, in a study by Addis et al. (2008) using the adapted AI, the authors compared younger and older adults on their ability to reconstruct personally experienced events from the past, and simulate novel future events that they may experience in their personal future. The temporal distances of the cues were constrained so that participants generated descriptions of events within the “past/next few weeks/years”. Relative to the younger adult group, the older adults produced fewer internal details when remembering the past or imagining the future. This age-related decline in episodic foresight was also reported in subsequent studies by Addis et al. (2010) and Rendell et al. (2012). Interestingly, these two investigations explained this impairment differently. First, Addis et al. (2010) attributed the compromised ability to project into the future to a breakdown in the recombination of past information into a novel future scenario. However using a different paradigm, Rendell et al. (2012)’s results suggested that a specific impairment in the capacity for self-projection, which is the capacity to shift one’s current perspective of the immediate environment to a different spatial, mental, temporal alternative was the underlying contributor. However despite differences in interpretation, the literature has consistently highlighted that both episodic memory and episodic foresight are similarly

impacted across stages of development, therefore suggesting neurocognitive overlap between these two abilities

3.6.2 Neurological evidence

Apart from the findings from developmental studies, a second source of evidence for a relationship between episodic memory and episodic foresight comes from neurological studies. For example, early evidence for this link between past and future MTT is provided by Patient K.C who was the victim of a motorcycle accident at the age of 30 which caused extensive brain damage to a number of cortical and subcortical regions resulting in severe amnesia (Tulving, 2002). Despite being able to provide many facts about the world and his life, Patient K.C was unable to remember subjective experiences of his life, or imagine himself in the future. It was concluded that his inability to place himself within either temporal context demonstrated insufficient autonoetic consciousness, the defining element of episodic memory and episodic foresight. This parallel deficit therefore indicated possible neurological overlap between past and future MTT. However, the most explicit evidence of the overlap between past and future MTT has resulted from the advancement of neuroimaging technology. Investigations exploring possible parallels in brain activity during simulation of past and future events were initiated by Okuda et al. (2003) and since then numerous imaging studies have followed suit. The following section will discuss evidence from three pivotal investigations supporting the neurological overlap between episodic memory and episodic foresight.

In the first, Okuda et al. (2003) used PET and observed activation within the prefrontal cortex and two MTL structures (hippocampus and parahippocampal gyrus) when healthy adults freely recalled and imagined events in the near or far past or future. The MTL is a region that is widely known to be involved in learning and memory processes (Squire, Stark, & Clark, 2007). The hippocampus is one of the key structures of the MTL and is

thought to be responsible for combining disparate elements for the construction of mental scenarios (Hassabis & Maguire, 2009). Studies that have assessed episodic foresight ability in amnesic patients with known MTL or hippocampal specific atrophy have demonstrated comparable impairments in episodic memory and episodic foresight ability. This not only reinforces the overlap between the two capacities, but also strengthens the argument for the importance of this area and embedded structures for MTT.

Similar to Okuda et al. (2003), subsequent investigations by Szpunar, Watson, and McDermott (2007) and Addis et al. (2007) also observed overlapping activity within the prefrontal cortex and hippocampal regions during both past and future even simulation. While Okuda et al. (2003) required patients to freely recall/imagine past/future events, Szpunar et al. (2007) and Addis et al. (2007) administered event cues to prompt participant recall and future simulation. In the Szpunar et al. (2007) study healthy adult participants were instructed to recall a past event, imagine a future event, and also imagine an event involving well-known past American president Bill Clinton (which was devoid of any MTT demand). *fMRI* data identified overlapping neurological activity within prefrontal and hippocampal regions, as well as activation within the posterior midline region around the precuneus when recalling the past and imagining the future event. However, this activation was not present when participants imagined the event relating to Bill Clinton. This finding suggests a neurological profile specific to MTT into one's personal past and future.

Addis et al. (2007) also used *fMRI* to investigate the neural substrates of episodic foresight but extended this exploration to differentiate the neurological activity between the construction and elaboration phases proposed in the constructive episodic simulation hypothesis. While lying in a scanner, participants were visually presented with a cue word and instructed to silently generate a past or future event to describe (construction). Following this, participants were instructed to silently recall or imagine the personal event in as much

detail as possible (elaboration). Addis et al. (2007) identified neurological overlap between past and future event descriptions during both the construction and elaboration phases. In relation to the construction phase, activation in visuospatial and left hippocampal regions was observed during the construction of both past and future event simulation. It was posited that the activation of the left hippocampus in the early stages of event construction was due to the interaction between the visually presented event cues and memory retrieval processes involved in searching for and recovering autobiographical memories needed to construct the past and future mental scenarios.

The magnitude of neurological overlap however was far greater during the elaboration phase. More specifically, during the elaboration phase, extensive overlap between past and future event simulation was identified in the left medial PFC which was expected given that this region is known for self-referential information and that participants were explicitly instructed to simulate personally relevant past and future events. Widespread activation in the bilateral parahippocampal and retrosplenial cortices, posterior cingulate and precuneus was also observed when elaborating event details during past and future conditions. These regions are also known to support contextual processing, self-reflection, integration of emotions and memory, and episodic imagery; all of which can support the elaboration of details related to a personal event. Particularly interesting however was the finding that right hippocampal activation was additionally observed during future event construction but not past event reconstruction. This differential activation of the right hippocampus was attributed to the integration of disparate details into a future event, which is an additional demand not required for memory recall.

Overall, despite slight variations in assessment across these investigations, it appears that activation within the prefrontal cortex and MTL structures have been consistently observed during memory recall and future event simulation, reinforcing the idea of a specific

core network that is involved in mental time travel into the past and future (Addis et al., 2007; Okuda et al., 2003; Szpunar et al., 2007).

3.7 Other processes involved in episodic foresight

Although there is strong support for the role of episodic memory in episodic foresight, episodic foresight involves more than recalling the past and thus requires more cognitive effort (Arnold, McDermott, & Szpunar, 2011). Evidence for the additional processing requirements of episodic foresight is provided by studies of clinical populations that have demonstrated asymmetric performance on episodic memory and foresight tasks, with episodic foresight impairments not shown to be secondary to episodic memory impairment (de Vito et al., 2012; Irish, Addis, Hodges, & Piguet, 2012). Other abilities that have been proposed to contribute to episodic foresight include executive functioning (D'Argembeau et al., 2010; Suddendorf & Corballis, 2007). This is because episodic foresight requires the flexible manipulation of past information into a new time period and it also involves the capacity to inhibit the simple recasting of retrieved memories (Schacter & Addis, 2007). In addition, processes such as scene construction, self-projection, and narrative ability have also been implicated in episodic foresight ability (Buckner & Carroll, 2006; Gaesser, Sacchetti, Addis, & Schacter, 2011; Hassabis, Kumaran, Vaan, et al., 2007). Each of these will now be considered in detail in terms of their respective contribution to episodic foresight.

3.7.1 The role of executive functions in episodic foresight

Executive functions refer to higher-order cognitions that involve multiple processes and complex brain networks (Carpenter, Just, & Reichle, 2000). These higher-order cognitions are goal directed and allow for adaptive planning and successful problem solving (Carpenter et al., 2000). Executive functions include planning, inhibitory control, task switching, cognitive flexibility and performance monitoring, with deficits in such processes

indicative of frontal lobe dysfunction (Carpenter et al., 2000). Given the identified involvement of prefrontal regions in both episodic foresight and executive processes, as well as the complex nature of episodic foresight, it has been suggested that the ability to mentally project into the future is at least to some extent reliant on these higher-order cognitions (Addis et al., 2007; Buckner & Carroll, 2006; D'Argembeau et al., 2010; Suddendorf & Corballis, 2007). However, despite this sound rationale, the exact role of executive processes in episodic foresight is largely unknown. Indeed, there is limited research directly investigating the role of executive function in episodic foresight, and the research that has been conducted reports inconsistent findings.

One of the few studies that has explored the role of executive processes in the capacity to mentally simulate novel future scenarios was conducted by D'Argembeau et al. (2010). In that study, the authors attempted to identify the individual contributions of a range of possible component processes that might be involved in episodic foresight including executive processes. Executive functioning was indexed by performance on verbal and non-verbal fluency tasks. These two tasks were combined following principal components factor analysis before being correlated with measures of episodic foresight. Fluency tasks impose particular demands on executive processes in order to initiate, organise and monitor the retrieval of information. The findings from D'Argembeau et al. (2010) identified involvement of executive processes in the recall of episodic memories as well as in the simulation of novel future scenarios. However there was a differential finding, with executive processes correlating with the level of specificity in event details only when describing future events and not when describing past events. The interpretation of these findings by D'Argembeau et al. (2010) was twofold. First, they concluded that executive processes appear to play a general support role in “accessing and representing autobiographical knowledge” (pg. 816). Second, unlike pre-experienced memories of the past, future events are not restricted to any

particular spatiotemporal context and as a result there are an infinite number of possible future experiences that can be simulated. Consequently, the construction of novel future events would require multiple searches within memory stores in order to retrieve specific details unique to the future event being constructed. Also, monitoring of information being searched through within memory stores is necessary for future simulation in order to differentiate between relevant and irrelevant details. This is different to the retrieval of past experiences as these events have a precise spatiotemporal signature, which would not require as many search cycles, therefore not requiring the level of support from executive functions as imagining the future.

Investigations of clinical groups with specific neurological atrophy and identified episodic foresight impairment have also provided evidence for the role of executive processes in the capacity to project the self into the future. A study by de Vito et al. (2012) of 32 patients diagnosed with Parkinson's Disease (PD) supported the findings of D'Argembeau et al. (2010). de Vito et al. (2012) used a reduced version of the adapted AI (16 cue words as opposed to 32) to assess mental simulation of past and future events, and also included an atemporal condition to assess the patients' capacity to construct mental scenes in the absence of any temporal element. This condition involved providing participants with short verbal sentences defining ordinary scenarios (e.g. *Imagine you are standing in an open field by the banks of a river*) and instructing them to provide a description of that experience in as much detail as possible. Executive function was measured using the Frontal Assessment Battery (FAB) (Dubois et al., 2000). This tool assesses six cognitive processes related to frontal lobe functioning including conceptualization of knowledge, mental flexibility, and inhibitory control. The findings of this investigation demonstrated that relative to a healthy control group, the PD patients had a selective impairment in episodic foresight, which was not secondary to episodic memory impairment or the inability to construct atemporal mental

scenarios. Instead, the authors attributed the episodic foresight deficits to executive dysfunction. This claim was strengthened by further investigation of a subset of seven PD patients who performed the poorest on the episodic foresight task and who were then compared to the rest of the group. The groups were compared on their performances on the Frontal Assessment Battery performance and findings demonstrated that these seven patients had significantly poorer executive functions than the rest of the group.

It was posited by de Vito et al. (2012) that although PD patients were able to access and retrieve memories that could be used to construct novel future scenarios, they were unable to suppress the prepotent tendency to simply recall past. The authors suggested that this resulted in compromised ability to assimilate past information into construction of the future. They attributed this lack of ability to fragment retrieved memories for use in future event construction to reduced executive processes.

A second study indicating a possible link between executive processes and episodic foresight was conducted by Squire et al. (2010). They administered the adapted AI to a sample of patients with lesions that were limited to the hippocampus. Given that the hippocampus is one of the key structures that comprise the core network arguably underpinning MTT (Schacter et al., 2007), it was postulated that atrophy in this region should produce specific impairments in MTT. However, the authors found that the patients' capacity to reconstruct autobiographical memories and simulate plausible future events was intact and therefore suggested that impairments in simulating the future were attributable to neurocognitive dysfunction outside of the hippocampus, including frontal cortices which are involved in executive processing. The authors concluded that the hippocampus is not as crucial to MTT as it had been widely accepted, and that declines in the capacity to reconstruct the past or construct one's personal future can be attributed at least in part to dysfunction in areas that govern executive processes.

Further potential support for the involvement of executive processes in episodic foresight was provided by Irish, Hodges, and Piguet (2013). Also using the adapted AI, the authors assessed patients with the behavioural variant of frontotemporal dementia (bvFTD) on their capacity for past and future event simulation. This neurodegenerative disorder had previously been linked to significant declines in a number of cognitive processes including autobiographical memory, which were attributed to executive and frontopolar dysfunction, but episodic foresight had not been investigated. This investigation identified an episodic foresight deficit within the context of bvFTD and also identified a neurological distinction between past and future event simulation. Specifically, recollection of past memories was reliant on the medial PFC, whereas the simulation of future events was driven by frontopolar, lateral temporal, and medial temporal areas. These findings not only provide evidence for the increased cognitive demand of episodic foresight relative to episodic memory, but also for the involvement of frontal regions in the capacity for future thought which also underpin executive processing. However, it should be noted that in this study performance on past and future event simulations did not correlate with measures of executive processes including the Verbal Letter Fluency test, the Trail Making test (cognitive switching), and the Hayling Sentence Completion test (cognitive inhibition). The authors suggested that the neuroimaging findings reinforced the notion that episodic foresight is a complex ability that requires the involvement of various cognitive processes. However the lack of significant association between episodic foresight and performance on executive functioning measures led the authors to suggest that the higher-order cognitions needed for future event simulation may not have been assessed in this particular investigation.

A lack of association between episodic foresight and executive functioning has however also been reported in some other clinical groups with compromised episodic foresight ability. For instance, although Addis et al. (2008) speculated about the involvement

of executive processes in the age-related declines in episodic foresight, correlational analyses did not reveal significant relationships between measures of executive processes and future event simulation. Furthermore, in a study of patients with Post Traumatic Stress Disorder no association was found between the ability to project into the future (as measured by the adapted AI), and executive functioning (verbal fluency) in either the clinical or the control group (Brown et al., 2014). Child studies have also produced similar findings. For example, given that episodic foresight requires the capacity to switch between and compare different memories before electing the most relevant to be used in the simulation of a future event, Terrett et al. (2013) used a measure of cognitive switching from the executive function domain of the NEPSY II in their study of MTT in children with Autism Spectrum Disorder (ASD). Although the ASD group demonstrated compromised MTT into the past and future, there were no differences in executive functioning as indexed by cognitive switching, and it did not contribute to episodic foresight in either the clinical or the control group. Similarly, another study of children's capacity for episodic foresight revealed a lack of correlation between a measure of executive processing and episodic foresight after controlling for age and general cognitive ability (Hanson, Atance, & Paluck, 2014).

The inconsistent findings to date relating to the role of executive functions in episodic foresight may be attributed to a number of factors, particularly relating to variations in methodology. First, although many studies employ the use of the adapted AI, a number of modifications have been applied across investigations. For instance, there are differences in the use of, types, frequency, and administration of cues. Second, across the studies the number and type of assessments employed to measure executive processes vary significantly which may contribute to the differences in findings. For example, D'Argembeau et al. (2010) used measures of verbal fluency to represent executive processes and found that this ability contributed to episodic foresight, whereas Terrett et al. (2013) administered one measure of

executive functioning (assessing switching) and did not find any association between any of the executive processes and episodic foresight in a group of autistic children or the typically developing comparison group. These methodological differences therefore reduce the ability to make direct comparison between studies and their findings.

Despite the variability in findings regarding the role of executive functioning in episodic foresight, it is generally accepted that it is a complex process which requires the involvement of a number of cognitive abilities in order to create, mentally project, and pre-experience a novel future event. Although the roles of episodic memory and executive processes have been a focal discussion points within the literature, other possible contributors have also been proposed including the capacities of scene construction and self-projection (Buckner & Carroll, 2006; Hassabis, Kumaran, & Maguire, 2007; Hassabis, Kumaran, Vaan, et al., 2007; Suddendorf & Corballis, 2007). Although both of these abilities have been implicated in episodic foresight ability, the development of the now widely used paradigm by Hassabis, Kumaran, Vaan, et al. (2007) has allowed for the deconstruction of identified episodic foresight deficits in various clinical groups which helps shed light on their relative contributions.

3.7.2 Self-projection, scene construction, and narrative ability

Buckner and Carroll (2006) place particular focus on the process of self-projection as being important for a number of mental processes including episodic memory, episodic foresight, spatial navigation, and theory of mind. Self-projection refers to the ability to shift between one's current perspective of the immediate environment and a different spatial, mental, or temporal alternative. However this proposal has been described as somewhat broad and does not specifically apply to MTT. Suddendorf and Corballis (2007) refined the concept of self-projection by focusing on the specific capacity to project oneself backwards and forwards in time, rather than simply changing one's perspective. This emphasis on the

capacity to project the self through time is reminiscent of the proposal by Tulving (1985) that MTT requires an awareness of the self within different temporal dimensions.

In contrast, Hassabis, Kumaran, Vaan, et al. (2007) proposed a theory that acknowledges, but de-emphasizes the involvement of self-projection for cognitive faculties including episodic memory and episodic foresight and instead places most focus on the ability for scene construction. Scene construction refers to the process of building an imagined scenario in our mind. Hassabis, Kumaran, Vaan, et al. (2007) proposed that scene construction is the common underlying process that episodic memory and episodic foresight rely on. Scene construction can be differentiated from simple visual imagery as it involves mentally generating and combining multiple elements such as contextual details, sensory details, thoughts, people, and objects, in order to create a coherent, spatial representation of an imagined scene (Hassabis, Kumaran, & Maguire, 2007; Hassabis, Kumaran, Vaan, et al., 2007). Hassabis, Kumaran, and Maguire (2007) have argued that scene construction and self-projection abilities are governed by two discernible neurological substrates, and suggest that the hippocampus is primarily responsible for scene construction (in terms of combining disparate information retrieved from memory systems), and the anterior medial prefrontal cortex, posterior cingulate gyrus, and precuneus are responsible for the capacity to project the self through time and other self-referential processes involved in MTT. Hassabis, Kumaran, and Maguire (2007) do however acknowledge the involvement of self-projection and other self-referential processes in episodic memory and episodic foresight but suggest that these self-referenced components are *additional* contributions to the basic ability to construct mental scenes, which is required for a number of cognitive operations such as planning, imagination, and navigation.

Referring to the capacity to verbally communicate mental simulations effectively, narrative ability is another processes proposed to be involved in mental time-travel

(Corballis, 2009). However the contribution of narrative ability for mental-time travel is currently not fully understood. Race, Keane, and Verfaellie (2011, 2013, 2015) assessed the narrative ability of amnesic patients with lesions restricted to the MTL. The authors observed that despite the amnesic patient's impoverished narrative ability when describing past memories or novel future experiences, their narrative ability when describing an event based on pictorial cues remained intact. This was evidenced by the comparable number of episodic details generated by the patients relative to healthy control groups (Race et al. 2011, 2013). Despite subsequent findings identifying qualitative differences in these narratives, where descriptions by the amnesic patients were less coherent (Race et al. 2015), the authors concluded that deficits in mental time travel displayed by amnesic patients are not secondary to impaired narrative ability (Race et al. 2011, 2013). In contrast, Zeman, Beschin, Dewar and Della Sala (2013) did report impaired narrative ability of amnesic patients in comparison to a healthy control group. However, their sample of amnesic patients was not as homogenous as the sample recruited by Race et al (2011, 2013, 2015), with additional lesions outside of the MTL, and cognitive impairments in domains other than memory. These studies have provided further evidence for the role of the MTL in mental time-travel, but highlight the need for more exploration of the contribution of narrative ability to this ability within healthy and clinical groups. Many studies that attempt to differentiate the contributions of each of these processes use the paradigm developed by Hassabis and colleagues. The following section will explain this paradigm in more detail.

3.7.3 Disentangling episodic foresight deficits using the paradigm developed by Hassabis, Kumaran, Vaan, et al. (2007)

As previously noted, many investigations relating to the episodic foresight ability in adults have used cue word interview type formats that have required descriptions of past and future events (e.g. Adapted AI). However, in their investigation assessing bilateral

hippocampal amnesic patient's ability to imagine new experiences, Hassabis, Kumaran, Vaan, et al. (2007) developed an imagination task to explore the involvement of different component processes. Similar to the Adapted AI, this paradigm uses verbal cues as prompts. However instead of asking participants to recall previously-experienced past events and imagine themselves experiencing future events in response to single words, participants are instructed to complete three imagination tasks based on scenario cues for one atemporal event, a future event, as well as complete a narrative task. Also like the Adapted AI, participants are instructed to imagine and describe themselves experiencing these situations. By adopting this approach Hassabis, Kumaran, Vaan, et al. (2007) suggested it would be possible to disentangle the contributions of scene construction and self-projection to the imagination of new experiences

3.6.3.1 Hassabis, Kumaran, Vaan, et al. (2007) paradigm cues

As noted, this paradigm is comprised of three types of scenario cues. The *atemporal* event condition involves participant reorganizing the existing information from memory to create a novel, fictitious scenario in a familiar context (e.g. drinking a coffee in a pub/bar). This does not require MTT and therefore arguably reflects scene construction ability. In fact, participants are explicitly instructed not to simply recall an actual pre-lived experience of being in the scenario. While it could be argued that the imagination of everyday scenes relies on recent episodic memories, the use of familiar, commonplace, scenarios as cues was specifically selected because knowledge of these scenarios is based on semantic information which has been collected over time through one's experience. Therefore participants are able to generate a mental construction without needing to relate it to a specific personal experience. The *future* event condition explicitly instructs participants to imagine experiencing a possible event in the future (e.g. Imagine how you will spend next Christmas). Unlike the atemporal cues, the future cues have an additional demand for MTT, and therefore

require auto-noetic consciousness. Finally, the *narrative task* provides participants with a story structure on which to base their description of an event. Similar to the atemporal task, the narrative task requires scene construction ability but has no MTT demand; therefore it does not require auto-noetic consciousness. However the difference between the narrative and atemporal tasks is that the narrative task makes the lowest demands on imagination by providing the participant with a detailed story structure on which to base their description. The inclusion of the narrative task therefore provides an important means of testing whether any difficulties on this interview-format task simply reflect poor narrative ability.

Although all three conditions are self-referent and require some degree of scene construction, the variations between the three tasks allow the disentangling of which abilities might be specifically compromised in episodic foresight. For instance, the future condition is the only task that involves the additional element of imagining a subjective sense of self in time (auto-noetic consciousness) and therefore difficulties on this task in comparison to the other two would suggest that episodic foresight deficits reflect particular problems with the self-projection component of this process. The original protocol involves six atemporal, three future, and one narrative cue (see Table 1) but a number of studies have administered variations of the paradigm to clinical groups with already established impairments in episodic foresight when attempting to disentangle the roles of scene construction and self-projection in that ability (D'Argembeau et al., 2010; de Vito et al., 2012; Lind, Williams, Bowler, & Peel, 2014; Raffard et al., 2010). This paradigm has been valuable in highlighting the fact that deficits in either scene construction or self-projection can lead to impaired episodic foresight ability.

Table 1.

Details of the 10 Scenario Cues used in the original Hassabis Paradigm

Atemporal scenarios	1. Imagine you're lying on a deserted white sandy beach in a beautiful tropical bay
	2. Imagine you're standing in the busy main hall of a museum containing many impressive exhibits
	3. Imagine you're sitting having a drink in a pub
	4. Imagine you're standing in on the deck of a ship that's pulling out of port on the beginning of a voyage
	5. Imagine you're standing by a small stream somewhere deep in a forest
	6. Imagine you're standing in the middle of a bustling street market
Future scenarios	7. Imagine something you will be doing this weekend, but just give me one event
	8. Imagine how you will spend next Christmas
	9. Imagine the next time you'll meet a friend
Narrative scenario	10. Imagine you are standing in the middle of the impressive high vaulted entrance hall of a mediaeval castle. There is a tower somewhere in the castle, the top of which is accessed via a circular winding staircase. I want you to describe to me in as much detail as possible your route through the castle's many rooms and floors until you reach the top of the tower. Use all your senses including what you see, feel, and do on the way to the tower.

3.7.4 Evidence of a link between episodic foresight impairment and scene construction deficits

Hassabis, Kumaran, Vaan, et al. (2007) were the first to demonstrate an association between episodic foresight impairment and scene construction deficits in a group of amnesic individuals with bilateral hippocampal damage. Not only were patients in this study unable to recall the past or imagine novel future experiences, but Hassabis, Kumaran, Vaan, et al. (2007) also observed no difference between the ability to construct atemporal and future scenarios. This finding led the authors to conclude that the hippocampus mediates the capacity for scene construction by supporting the binding of disparate elements of an experience into a holistic scenario, which is a key function that underpins MTT into the past and future.

Raffard et al. (2010) provided further support for the role of scene construction in episodic foresight. First, these authors confirmed the schizophrenia-related episodic foresight deficit established by D'Argembeau, Raffard, et al. (2008). Second, the schizophrenia group performed less well on both the scene construction and self-projection conditions of the Hassabis, Kumaran, Vaan, et al. (2007) paradigm, relative to healthy control participants, but they did not find the future condition any more difficult than the atemporal condition. This led to the conclusion that impairments in MTT within the context of schizophrenia were at least in part attributable to deficits in scene construction ability.

Individuals with ASD represent another clinical group that has been investigated in relation to episodic foresight and its underlying mechanisms. For example, Lind and Bowler (2010) initially observed parallel deficits in episodic memory and foresight abilities within the context of high-functioning ASD. Although both the control and ASD groups found future event simulation more demanding than memory recall, the adults diagnosed with ASD demonstrated compromised abilities in the recall of past episodic memories and imagination of novel future personal event details relevant to normal controls. Lind and Bowler (2010) postulated that this inability to MTT into the past and future might be explained by an failure to bind the separate bits of retrieved information into a holistic reconstruction of personal past events or simulation of plausible future events which are rich in contextual details. Lind and Bowler (2010) attributed this deficit to limitations in the episodic buffer within working memory. This refers to a mental space which provides a temporary storage facility where the binding of information from different memory systems occur (Baddeley, 1992). This process is strikingly reminiscent of Hassabis, Kumaran, Vaan, et al.'s (2007) description of the process of scene construction. In a subsequent investigation conducted by the same research group (Lind et al., 2014), adults diagnosed with high-functioning ASD completed an assessment similar to the original Hassabis, Kumaran, Vaan, et al. (2007) paradigm to assess

episodic foresight and atemporal scene construction, with the inclusion of a recall task to assess episodic memory. A separate task was also included to assess narrative ability. The findings of this investigation identified that the adults diagnosed with ASD had compromised ability across all domains. Relative to the control group, the adults with ASD were unable to recall personal past events (episodic memory), imagine plausible future events (episodic foresight), or imagine atemporal fictions events (scene construction). These deficits were not secondary to narrative ability as there were no differences in narrative task performance between the two experimental groups. The findings of impaired episodic memory and episodic foresight are similar to those of previous studies that have also demonstrated deficits in MTT within the context of ASD. However the particularly notable finding of this investigation was that the impairment in MTT in adults with ASD appeared to be underpinned by a diminished capacity for scene construction. Successful completion of all three experimental conditions required intact scene construction ability. Given that the ASD group demonstrated compromised ability across all three conditions, the findings provide evidence that basic scene construction ability appears necessary for MTT in both temporal directions and that impairment in this basic process may be sufficient to cause ASD related deficits.

3.7.5 Evidence that episodic foresight impairment can be linked to self-projection deficits

While a theoretical rationale can be posited, the empirical evidence supporting a role for self-projection in episodic foresight is scarce. Indeed only one study with older adults has reported a link between deficits in simulating future experiences and specific impairments in self-projection (Rendell et al., 2012). In this study Rendell et al. (2012) administered the original protocol developed by Hassabis, Kumaran, Vaan, et al. (2007) to a group of young (18 to 27 years old) and a group of older (65+ years old) adults in order to disentangle age-

related differences in episodic foresight. As expected, relative to the younger adults the older adults performed less well on all of the imagination tasks (narrative, scene-construction, and self-projection). However the ability to provide contextually rich descriptions of future scenarios was disproportionately impaired in the older group. Thus this study not only identified age-related declines in episodic foresight but also showed that this deficit appeared linked to compromised self-projection ability.

The literature relating to episodic foresight in the context of clinical groups, and the components that underpin this ability is not clear-cut. Evidently there is a need for future studies to clarify not only which clinical groups are impaired in this ability, but also to identify what underpins these difficulties if we are to offer more effective support.

Chapter 4: Introduction to Article 1

4.1 Title

Episodic foresight deficits in long term opiate users

4.2 Objectives

There is strong evidence demonstrating adverse neurocognitive outcomes within the context of chronic opiate use which give rise to impairments in cognitive processes that are imperative to adaptive independent living. Neuroimaging studies have identified structural and functional abnormalities within the prefrontal and temporal regions which are areas heavily involved in higher-order cognitions and memory, respectively. Although there are a number of cognitions associated with long-term opiate use, episodic foresight, a cognition closely related to memory, has not yet been directly assessed in any substance-using population.

Referring to the capacity to mentally time travel into the future and pre-experience novel scenarios, episodic foresight has demonstrated significant adaptive value as it allows for the construction of scenarios in our mind's eye which can be hypothetically worked through before execution. The literature has provided strong evidence that this complex ability is reliant on episodic memory to provide the building blocks for future event construction; as well as executive control to assist in the assimilation of retrieved information. Episodic foresight can play a role in the planning of future goals as well as within decision making processes which see the fulfilment of long term needs given priority over choices leading to short term or immediate gratification.

A breakdown in episodic foresight may cause significant difficulties in everyday functioning given that the frequency of future-oriented thoughts outweighs thoughts that require recall of past experiences. This could pose particular difficulties for individuals being

treated for substance dependence. Indeed, compromised episodic foresight ability may help explain, at least in part, the extremely high relapse rates associated with chronic opiate use, given that many relapse prevention protocols heavily rely on future-oriented thinking.

The primary aim of this first study was to directly assess episodic foresight ability in the context of chronic opiate use. The secondary aim was to explore whether any identified deficit could be attributed to impaired episodic memory and/or executive control given the neurological overlap with memory, and evidence suggesting involvement of complex higher-order cognitions in this ability.

4.3 Method

To assess episodic foresight the Adapted Autobiographical Interview was administered to 45 opiate-dependent individuals currently engaged in opiate substitution treatment, and 45 demographically matched control participants. The primary eligibility criterion for the opiate user group was current enrolment in an opiate substitution program (e.g. methadone). The opiate user group was recruited from Melbourne-based pharmacies and health services which dispensed opiate substitution treatment. Control participants were recruited from the general population through social contacts of the researchers.

Three measures of executive control were completed by all participants and episodic foresight was assessed using the Adapted Autobiographical Interview, which also provided an index of episodic memory. Participants were required to recall and describe events from their personal past (episodic memory) as well as construct novel future scenarios (episodic foresight). Interviews were independently transcribed and then scored for two types of details. Higher numbers of internal (episodic, related to event being described) details produced in the future conditions indicated better episodic foresight ability.

4.4 Results

Relative to controls, the opiate use group generated significantly fewer internal details when imagining the future but not when recalling the past. The opiate group performed less well than controls on only one measure of executive function which assessed cognitive inhibition. The results also provided support for the overlap between episodic memory and episodic foresight with significant relationships found for both experimental groups. However contrary to some previous literature no relationships between episodic foresight and executive control were found.

4.5 Conclusions

This study is the first to directly assess episodic foresight ability in the context of substance use. The findings suggest that although this group were capable of retrieving past details, they were not able to assimilate that information to construct novel future scenarios. These findings may have implications for the modification of relapse prevention strategies that rely on future-oriented thought processes. The absence of memory impairment despite the observed episodic foresight deficit in the opiate group also paves the way for future research to explore other factors contributing to this compromised ability.

CHAPTER 5: Article 1

Episodic foresight deficits in long-term opiate users

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Appendices

Appendix B: Participant Recruitment and Informed Consent

Appendix C: Background Measures

Appendix D: Measures of Executive Functioning

Appendix E: Hospital Anxiety and Depression Scale

Appendix F: Adapted Autobiographical Interview Script

Appendix H – 1: Confirmation of Study 1 Acceptance

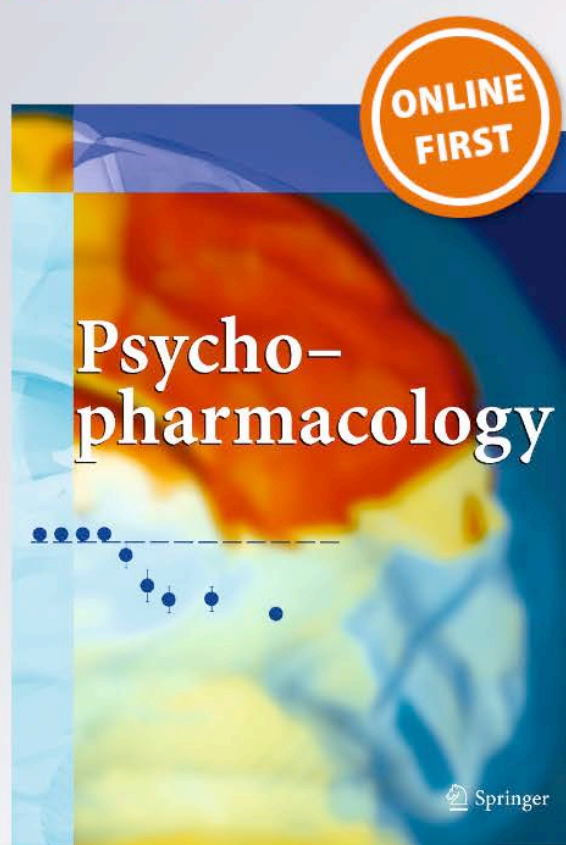
*Episodic foresight deficits in long-term
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Episodic foresight deficits in long-term opiate users

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Abstract

Rationale There is considerable literature showing that opiate use is associated with a range of neurocognitive deficits, including deficits in executive control and episodic memory. However, no study to date has assessed whether these neurocognitive difficulties extend to the ability to mentally time travel into one's personal future. This is a surprising omission given that executive control and episodic memory are considered to be critical for episodic foresight. In addition, opiate-related brain changes have been identified in the neural regions that underlie the capacity for episodic foresight.

Objective In the present study, we assessed how episodic foresight is affected in the context of chronic opiate use, as well as the degree to which any deficits are related to difficulties with executive control and episodic memory.

Methods and Results Forty-eight long-term heroin users enrolled in an opiate substitution program and 48 controls were tested. The results showed that, relative to controls, the clinical group exhibited significant impairment in episodic foresight but not episodic memory (as indexed by an adapted version of the Autobiographical Interview). For executive function, the clinical group was impaired on only one of three measures (Inhibition).

Conclusions These data provide important preliminary evidence that episodic foresight might be particularly susceptible to the neurocognitive effects of opiate use, as the difficulties identified were not secondary to more general executive control or episodic memory impairment. Because a number of widely used relapse prevention protocols require the ability to mentally project into the future, these data have potentially important practical implications in relation to the treatment of substance dependence disorders.

Keywords Episodic foresight · Opiate users · Autobiographical Interview · Executive functions · Episodic memory

Introduction

There is now a considerable literature showing that chronic opiate use is characterized by prominent neurocognitive impairment, particularly in prefrontal and medial temporal structures (Cheng et al. 2013; Ersche et al. 2006; Fu et al. 2008; Liu et al. 2009). Consistent with this pattern of neuropathology, opiate use has also been associated with deficits on behavioral measures of executive functioning and episodic memory, cognitive abilities that are known to impose particular demands on prefrontal and medial temporal neural substrates, respectively (Fernández-Serrano et al. 2011; Verdejo-García and Pérez-García 2007; Verdejo-García et al. 2007).

Episodic foresight is a critically important cognitive ability that may also be impaired in opiate users because of its reliance on prefrontal and medial temporal neural regions. Referring to the specific capacity to mentally travel forward in time, episodic foresight has immense survival value due to its anticipatory nature. Being able to project oneself forward in time allows for mental rehearsal of behaviors before selecting the action that will lead to a desired outcome (Suddendorf and Corballis 2007). D'Armentau et al. (2011) highlighted the prominent role thinking about the future plays in everyday

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life, reporting that the frequency of future-oriented thoughts outweighs those about the past, with a future thought occurring every 16 min. Episodic foresight has been consistently linked to independent living and a wide variety of functional behaviors (Suddendorf and Henry 2013) and thus deficits in this ability can have profound consequences. Indeed, a reduced capacity for episodic foresight has now been linked to functional difficulties in a number of clinical groups (D'Argembeau et al. 2008; Lind and Bowler 2009; Sarkohi et al. 2011; Terrett et al. 2013).

A breakdown in episodic foresight therefore represents an important potential mechanism that may contribute to the poor functional, social, and economic outcomes often associated with chronic opiate use (Hser et al. 2009; Villeux et al. 2010). However, from the literature to date, it has only been possible to infer how the capacity for episodic foresight is affected in opiate users indirectly via assessment of cognitive processes that incorporated some element of future thought, for example, planning, decision-making, or prospective memory (Ersche et al. 2006; Grant et al. 2000; Rogers et al. 1999; Terrett et al. 2014). Since each of these related aspects of prospection was found to be disrupted, these data support the possibility that problems with episodic foresight may also be a neurocognitive feature of chronic opiate use. To the best of our knowledge, the present study provides the first direct test of this possibility.

The secondary goal of the present study was to clarify the extent to which any episodic foresight difficulties seen in the context of chronic opiate use are related to other cognitive difficulties. Pre-experiencing one's personal future is a complex process which is likely to rely on multiple cognitions. For example, it has been suggested that semantic memory, (Irish et al. 2012) which provides semantic knowledge for use in the formulation of a future scenario, and scene construction, which refers to the capacity to create an imagined scenario in our mind's eye (Hassabis et al. 2007), may both be important to engage in episodic foresight. However, particular attention has been paid to episodic memory which has been strongly implicated in the capacity to project the self into the future. According to the constructive episodic simulation hypothesis, episodic foresight relies heavily on the retrieval of personally relevant memories of the past (episodic memory) as these provide the basic building blocks for the construction of novel future experiences (Schacter et al. 2007). Episodic foresight however involves more than just memory recall and is thus more cognitively demanding (Arnold et al. 2011). For instance, it involves holding information in mind, manipulating that information flexibly, and inhibiting the tendency to simply retrieve actual memories (Schacter and Addis 2007). As such, it has been suggested that episodic foresight imposes substantial demands on executive control (D'Argembeau et al. 2010). Given that executive control and episodic memory have been shown in a number of studies to

decline in the context of opiate use as previously noted, we investigated the association between episodic foresight and both of these abilities.

Three predictions were made. First, it was anticipated that compared to demographically matched controls, long-term opiate users would be more impaired in episodic foresight. Second, it was predicted that long-term opiate users would show deficits in executive functioning and episodic memory. Finally, due to neurological overlap, it was anticipated that episodic foresight ability in both the clinical and nondclinical groups would be significantly correlated with both executive control and episodic memory.

Method

Participants

This study was approved by the Australian Catholic University ethics committee and conformed to the ethical standards set out in the 1964 Declaration of Helsinki. Forty-eight long-term opiate-users (years of opiate use, $M=13.89$, $SD=6.48$) aged 27 to 50 years ($M=37.56$, $SD=6.45$) were recruited as was a control group consisting of 48 adults aged 20 to 56 years ($M=36.73$, $SD=10.28$) with no reported history of alcohol or other drug dependence. The two groups did not differ significantly on gender, $\chi^2(1, 96)=1.12$, $p=0.289$. They were matched on age and years of formal education and premorbid IQ as measured by the National Adult Reading Test (Nelson 1982) (see Table 1). However, the opiate group reported higher levels of negative affect as measured by the depression and anxiety subscales of the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983).

The participants in the opiate-user group were currently enrolled in an opiate substitution program (Methadone $n=31$; Suboxone $n=16$; Naloxone $n=1$). The average dose of Methadone was 52.18 mg ($SD=37.91$) and Suboxone was 10.53 mg ($SD=7.88$). The frequency of participant-reported current substance use is displayed in Table 1. The opiate group was recruited using fliers distributed through pharmacies. Eligibility for the opiate group required a minimum of 2 weeks stability on an opiate agonist prior to testing and abstinence from opiate agonist use for at least 5 h prior to testing. The control group was recruited using personal networks.

Exclusion criteria for both groups included a previous or current neurological condition, a psychiatric disorder, a history of heavy alcohol use (defined as 28 standard drinks per week for men and 14 for women) (Australian National Health and Medical Research Council 2001), or a previous acquired brain injury. Participants were instructed to refrain from use of alcohol or illicit drugs in the 24 h prior to testing. Participants were sent a reminder text message at least 24 h prior to their testing time, and abstinence was confirmed via self report on

Table 1 Participant characteristics

	Control group n=48		Opiale group n=48		t(94)	d
	M	SD	M	SD		
Proportion of men (%)	58 %		69 %			
Age (in years)	36.73	10.28	37.56	6.45	0.48	0.09
Education (in years)	14.25	2.58	13.33	2.62	1.73	0.36
Estimated IQ	110.71	4.96	112.53	6.41	1.56	0.32
Mental health						
Depression	2.63	2.58	6.47	4.22	5.40**	1.09
Anxiety	5.55	3.61	8.36	4.25	3.50**	0.71
Executive function tests						
Verbal Fluency test ^a	62.36	14.11	58.43	15.13	1.32	0.27
Trail Making Test ^b (s)	31.76	16.41	42.22	35.71	1.84	0.38
Hayling ^c	5.85	1.25	4.99	1.48	3.04**	0.63
Frequency of participants engaging in current substance use						
Nicotine ^d	14		38			
Alcohol ^e	41		25			
Cannabis ^f	4		19			
Amphetamines ^f	2		16			
Cocaine ^f	2		—			
Benzodiazepines ^f	—		11			
Heroin ^f	—		20			

^aVerbal fluency score represents the sum of phonemic and semantic fluency scores

^bParticipant performance on TMT was measured by subtracting the time (s) taken for part A from part B

^cOverall scaled score

^dDaily frequency of nicotine use reported for both groups

^eWeekly frequency of alcohol use reported for both groups

^f'Less than once a month' frequency of use reported for control group whereas 'at least once a week' frequency of use reported for opiale group

d=Cohen's d index of effect size. Cohen (1988) defines effect sizes of 0.2 as small, 0.5 as medium, and 0.8 as large

**p<.01

the day of testing. Participants were also excluded if English was not their first language. All participants were reimbursed up to AU\$30 (1 USD\$30) for their time.

Materials

Executive function

Three measures of executive control were used that were particularly sensitive to mental flexibility, inhibitory control, and self-initiation, respectively. First, the Trail Making Test (TMT) was used as this has been shown to provide a sensitive measure of mental flexibility (Arbuthnott and Frank 2000). The TMT consists of two parts. Part A requires participants to draw one continuous line to connect 25 scattered circles numbered from 1 to 25 in increasing numerical order. Part B requires the participant to draw a line connecting numbers and letters in increasing and alternating order (1-A-2-B-3-C, etc.).

The TMT was administered according to the guidelines in Strauss et al. (2006). Each part is timed and recorded in seconds. Participant performance was measured by subtracting the time taken for part A from part B, with lower scores indicating better performance.

The second executive measure used was the Hayling sentence completion test. This is a two-part, timed, verbal task that was used in the present study because of its sensitivity to inhibitory control (Burgess and Shallice 1997). Part A requires participants to sensibly complete 15 sentences (e.g., "She called her husband at his ...[WORK]"). Part B (inhibitory control) requires participants to complete another set of 15 sentences with unrelated words (e.g., "The captain wanted to stay with the sinking ...[LIPSTICK]"). Performance is measured by tallying errors and total time taken (in seconds) to complete both parts, which is then converted to a scaled score. Administration and scoring complied with instructions provided in the testing manual (Burgess and Shallice 1997).

Finally, verbal fluency (both phonemic and semantic probes) was used as the third executive measure to provide an index of cognitive initiation (Strauss et al. 2006). For phonemic fluency, participants were instructed to generate as many exemplars of words beginning with the letters F, A, and S, excluding numbers, proper nouns, or the same word with a different suffix. Each probe was allocated 1 min. Total phonemic fluency was determined by subtracting errors from correct responses. To assess semantic fluency, participants were then instructed to generate as many names of animals as possible in one minute. Both measures have been shown to be very sensitive to frontal neural substrates and to be valid indicators of executive control (Henry and Crawford 2004).

Episodic foresight

This study employed an adaptation of Levine et al. (2002) Autobiographical Interview (AI) by Addis, Wong, and Schacter (2008). All administration, training of scorers, and scoring procedures closely followed the procedures of this adaptation. The AI is a semi-structured interview used to assess episodic and non-episodic content in two temporal phase conditions (past and future) and therefore provides an index of both episodic memory and episodic foresight. Participants are instructed to describe a previously experienced past event or a novel future event in response to a cue word. The events had to refer to a specific time and place, be less than 1 day in duration, and be described from the participant's subjective perspective, rather than that of an observer. Three minutes is allocated for each cue word response, with timing starting once the participant decides on an event.

AI cue words Six cue words were chosen from the "Affective Norms for English Words" list (ANEW; Bradley and Lang 1999). Guided by the ANEW valence ratings, we chose two positive (birthday, vacation), two negative (nightmare, accident), and two neutral (taxi, bench) words (valence ratings $M=8.0$, $M=2.0$, $M=4.8$, respectively). The mean frequency of word use for these positive, negative, and neutral words was similar (i.e., 32.5, 21, and 25.5, respectively). Three cue words (one of each valence) were administered for each temporal condition. Similar to other studies using this protocol (e.g., Irish et al. 2012), all three cues for one temporal condition were completed before administration of the three cues for the other temporal condition which allowed for a reduced cognitive load and greater facilitation of instruction comprehension. The order of cue words was counterbalanced within each temporal condition leading to six counterbalanced versions of the task.

AI testing sessions Three interviewers were trained to follow the AI administration procedure. Participants were provided with instructions that included a demonstration of an event description prior to administration of the test cues. Once the demonstration and all three events relating to one temporal direction were completed, this was repeated for the remaining temporal direction. Set prompts were provided when clarification of instructions or facilitation of further event description was required, for example, "please tell me more about what you were thinking, feeling and doing."

AI scoring Interview transcripts were scored following the standardized procedures outlined by Addis et al. (2008). Firstly, a central event was identified in the transcription for each cue word trial. Details were segmented and categorized as either internal (episodic details specific to the central event) or external (non-episodic details including repetitions, semantic information, and information not specific to the central event). The number of internal details generated for future events is the primary measure of episodic future thinking, and the number of internal details for past events indexes episodic memory.

Three independent scorers who were blind to project aims and participant group membership scored the transcripts. Training manuals were provided by Donna Addis, which included an annotated example of scoring and 20 scoring events. Inter rater reliability between the three scorers across the 20 training events was assessed on the basis of a two-way mixed-design analysis of variance (ANOVA) intraclass correlation analysis. Cronbach's alpha obtained with our three scorers was 0.98 for internal and 0.90 for external details. The three scorers coded portions of the full dataset, and each scorer was assigned an equal number of transcripts from both experimental groups.

Procedure

All participants provided informed consent and were all tested individually in one session of approximately 3 h duration, with breaks provided as needed. Administration of cognitive assessments was counterbalanced.

Data analysis

All statistical tests were two-tailed. An alpha level of $p<0.05$ was considered significant, and effect sizes were estimated using partial eta-squared (η_p^2). Data was screened for missing values and outliers. Little's MCAR test indicated that data was missing completely at random, $\chi^2(1)=1.12$, $p=0.173$; therefore, expectation maximization was used to replace missing values. Significant positive skewness within the interview data was rectified using logarithmic transformations.

Finally, verbal fluency (both phonemic and semantic probes) was used as the third executive measure to provide an index of cognitive initiation (Strauss et al. 2006). For phonemic fluency, participants were instructed to generate as many exemplars of words beginning with the letters F, A, and S, excluding numbers, proper nouns, or the same word with a different suffix. Each probe was allocated 1 min. Total phonemic fluency was determined by subtracting errors from correct responses. To assess semantic fluency, participants were then instructed to generate as many names of animals as possible in one minute. Both measures have been shown to be very sensitive to frontal neural substrates and to be valid indicators of executive control (Henry and Crawford 2004).

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Results

Background measures of cognitive functioning

Descriptive and inferential statistics for the verbal fluency, TMT, and Hayling are reported in Table 1. It can be seen that the only group difference to emerge was for the executive measure that was particularly sensitive to inhibitory control (Hayling). The opiate group performed significantly worse than the control group on this measure.

Autobiographical Interview (AI)

An independent samples *t* test found no significant differences ($p=0.731$) between the opiate ($M=374.70$, $SD=127.93$) and control ($M=373.60$, $SD=184.60$) groups on the total number of details generated across all six interview conditions, suggesting no differences in overall amount of verbal output.

The number of details generated for past and future events is displayed in Fig. 1 as a function of group status (opiate-user group, control), temporal direction (past, future), and type of details (internal, external). A mixed $2 \times 2 \times 2$ ANOVA was conducted for the number of details generated. The between-groups variable was group status, and the within-groups variables were temporal direction and detail type. Given the significantly higher levels of psychopathology reported in the opiate group, it seemed important to consider whether mental health issues may have had an impact on episodic foresight ability. No significant associations were evident between the outcome variable of future internal details with either depression or anxiety for both the control (all $p \geq 0.293$) and opiate (all $p \geq 0.237$) groups. Consequently, no statistical control for these variables was required for the ANOVA analysis (Tabachnick and Fidell 2006).

There was a main effect of temporal direction, $F(1, 94)=55.95$, $p<0.001$, $\eta_p^2=0.373$; however, there were no main effects of group status $F(1, 94)=0.12$, $p=0.731$, $\eta_p^2=0.001$, or detail type $F(1, 94)<0.01$, $p=0.999$, $\eta_p^2<0.01$. The two-way interaction of temporal direction and group status was not significant, $F(1, 94)=2.14$, $p=0.146$, $\eta_p^2=0.022$ but all other two-way interactions were group status and detail type, $F(1, 94)=26.76$, $p<0.001$, $\eta_p^2=0.222$ and temporal direction and detail type, $F(1, 94)=9.01$, $p=0.003$, $\eta_p^2=0.087$. The interaction between group status and detail type indicated that the control group generated a greater number of internal details than the opiate-user group but this pattern was the reverse in relation to external details. The interaction between temporal phase and detail type showed that greater internal details were reported in the past rather than in the future condition, supporting the notion that overall, episodic foresight requires more cognitive effort. There was also a three-way interaction, $F(1, 94)=6.63$, $p=0.012$, $\eta_p^2=0.066$.

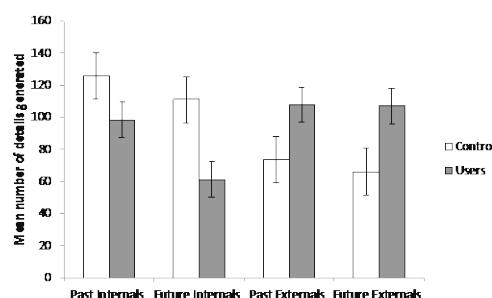


Fig. 1 The mean number of internal and external details generated on the AI as a function of group status (control group, $n=48$; opiate-user group, $n=48$) and temporal direction. (Error bars depict standard error of the mean)

The significant three-way interaction was further investigated with two 2 (group status) \times 2 (temporal direction) ANOVAs conducted separately for internal and external details.

Analysis of the number of internal details

This analysis revealed significant main effects of temporal direction $F(1, 94)=44.98$, $p<0.001$, $\eta_p^2=0.312$ and group status $F(1, 94)=8.23$, $p=0.005$, $\eta_p^2=0.080$. An interaction between temporal direction and group status $F(1, 94)=7.95$, $p=0.006$, $\eta_p^2=0.078$ was also found. This interaction was analyzed with tests of simple effects that revealed a simple main effect of temporal direction both within the control group, $F(1, 47)=7.55$, $p=0.007$, $\eta_p^2=0.074$ (medium effect size) and within the opiate-user group, $F(1, 58)=345.38$, $p<0.001$, $\eta_p^2=0.326$ (very large effect size). Figure 1 shows that both groups provided more internal details within the past condition than within the future but the difference was much larger for the opiate users. Further analysis of the interaction revealed a simple main effect of group status for future events, $F(1, 94)=11.64$, $p=0.001$, $\eta_p^2=0.110$, but not for past events $F(1, 94)=2.72$, $p=0.103$, $\eta_p^2=0.028$. Although overall the opiate group generated fewer internal details ($M=159.67$, $SD=85.18$) than the control group ($M=233.69$, $SD=170.12$), the difference in the future condition was larger than that in the past condition, see Figure 1.

Analysis of the number of external details

This analysis revealed a main effect of group status $F(1, 93)=14.662$, $p<0.001$, $\eta_p^2=0.136$. However, unlike the pattern for internal details, the opiate-user group generated more details than the control group. No main effect of temporal direction was found, $F(1, 93)=0.33$, $p=0.567$, $\eta_p^2=0.004$ or interaction between temporal direction and group status, $F(1, 93)=2.33$, $p=0.130$, $\eta_p^2=0.024$. Overall, the opiate users provided

significantly more external details ($M=215.02$, $SD=95.27$) than the control group ($M=139.90$, $SD=58.98$), irrespective of temporal direction.

Correlations with future thinking

The final analyses involved examining the relationships between episodic foresight (future internal details), episodic memory (past internal details), and the three measures of executive functioning for the two groups separately. It can be seen that the only significant relationship to emerge was between episodic foresight and episodic memory, which was seen in both groups ($r=0.56$ and 0.81 for the opiate users and controls, respectively). The Pearson product-moment correlations between episodic foresight and executive function are reported in Table 2.

Discussion

These data provide novel insights into how neurocognitive function is affected following chronic opiate use and specifically, provide the first direct assessment of how the critical capacity for episodic foresight is impacted. The results clearly indicate that relative to controls, episodic foresight is disrupted in this group, as operationalized by the generation of fewer episodic details when imagining novel future scenarios. Thus, although other studies have shown opiate-related deficits in related aspects of prospection, such as planning and prospective memory, these data provide evidence that the capacity for episodic foresight specifically is also adversely affected. The lower level of episodic details generated for the future condition reflects a core deficit in episodic future thinking among opiate users and is not simply a reflection of a generally lower level of verbal output. This is supported by the fact that the opiate group did not differ from controls on the total number of details generated when describing a future event but did differ on the type of detail. Specifically, the opiate-user group generated more non-episodic (i.e., external) details than episodic details despite explicit instructions in the Autobiographical Interview procedure to provide episodic details. Consistent with the view of Irish et al. (2011), it is therefore sug-

gested that an overproduction of external/non-episodic details is representative of "off-target" retrieval of memories, and in the context of the Autobiographical Interview, such responses are considered erroneous.

The potential functional implications of these findings are substantial. This is because episodic foresight has an anticipatory element which allows for the capacity to construct and work through various hypothetical scenarios before executing any goal-directed action (Suddendorf and Corballis 2007). Difficulties with this capacity may therefore limit the frequency of behavioral contingencies constructed, restricting choice of actions that would potentially achieve desired goals. In the context of chronic opiate use (and possibly other commonly abused drugs that are similar in their neurocognitive effects), impaired episodic foresight may therefore contribute to the maladaptive decision-making observed in this group that sees the fulfillment of current needs given priority over the meeting of future goals that may potentially yield greater rewards (Grant et al. 2000). Potentially inconsistent with this argument, however, in the present study, the two groups were equated on the Hayling inhibition task, a measure that taps into the restraint function of inhibition. Because different measures of inhibition are often uncorrelated with each other and are often differentially correlated with other cognitive functions (Kramer et al. 1994), future research should include more than one measure of inhibitory control to more rigorously assess this construct and how it relates to episodic foresight. Any reduction in this capacity is particularly meaningful when considered within the therapeutic context for this group. Specifically, given the goal-directed nature of episodic foresight, deficits could jeopardize therapeutic progress as many relapse prevention strategies require an element of future thought. Techniques such as goal setting, role playing how to decline future drug offers, and weighing up future consequences of achieving abstinence require projection to an unfamiliar future, free of narcotics. Therefore, in the absence of targeted cognitive rehabilitation techniques that focus on enhancing the capacity for episodic foresight, encouraging future-oriented thinking in the context of relapse prevention may have only limited efficacy.

The second major finding to emerge was that, for both the clinical and the control groups, generating episodic details in the future proved much more difficult than recalling episodic details from the past. This finding is consistent with other evidence suggesting that the construction of novel, future experiences requires more cognitive effort than the reconstruction of the past (Arnold et al. 2011; Okuda et al. 2003; Schacter et al. 2007). Moreover, the magnitude of the difference between remembering the past and imagining the future was much larger for the opiate-user group than the controls. This suggests that imagining one's personal future is particularly difficult for those with a history of prolonged opiate use. In addition, while some clinical groups have demonstrated

Table 2 Pearson product-moment correlations between episodic future thinking (future internal) and executive functions for each control and opiate-user groups separately

	Control group $n=48$	Opiate-user group $n=48$
Verbal fluency test	0.231	0.031
Trail Making Test	-0.183	0.036
Hayling	0.039	-0.044

deficits relative to controls in relation to both past and future temporal directions (Addis et al. 2008; Terrett et al. 2013), others have indicated a selective impairment in episodic foresight (Brown et al. 2014; de Vito et al. 2012; Duval et al. 2012; Irish et al. 2012) as was the case in the current study. This suggests that the deficit in episodic foresight shown by opiate users may not be attributable to problems accessing the memories required for future event simulation but instead may reflect difficulties with other abilities likely to contribute to episodic foresight such as scene construction (Hassabis and Maguire 2009) or semantic memory (Duval et al. 2012; Irish et al. 2012; Irish and Piguet 2013). The preservation of episodic memory but impaired foresight ability observed in the opiate group in our study suggests that intact episodic memory functioning, while it may be a contributor, is not sufficient for episodic foresight.

The third key contribution of this study was to provide insights into the neurocognitive correlates of episodic foresight difficulties in this population. As hypothesized, episodic memory and episodic future thinking were significantly correlated in both the clinical and nondclinical groups. This finding supports claims that episodic memory is an important contributor to episodic foresight and that both abilities may be served by similar neural and cognitive structures (Buckner and Carroll 2006; Hassabis et al. 2007). However, it is noteworthy that the strength of the correlation within the opiate group was weaker than that within the control group. Given that the two groups did not differ on episodic memory, the weaker correlation for the opiate group is also consistent with our suggestion that although they may be equally able to access the basic materials necessary for the construction of a future scenario, they may be less able to perform the other aspects of the process of episodic foresight not tapped by the present study. These data therefore reinforce the notion that, although important, episodic memory alone is not sufficient for future event construction. Also, contrary to predictions and some previous literature (D'Armenteau et al. 2010; de Vito et al. 2012), the correlational analyses in the current study showed that executive control, as operationalized by three distinct indicators of this construct, was unrelated to episodic foresight in both groups. These results therefore suggest that executive control may not be a core ability underpinning episodic foresight, although it is possible that executive control operations not assessed in the current study, for example, those more directly involved in retrieval (e.g., efficient organization), scene construction, or semantic memory, may be more pertinent for episodic foresight.

A noteworthy feature of the current study relates to the unexpectedly high level of functioning observed in the opiate-using group. As noted, they displayed only modest deficits in executive control relative to the control group, were community dwelling, and were not recruited from residential treatment facilities. Consequently, attendance at the testing session at a

university was reliant on participants' personal motivation to attend (and capacity to do so). Secondly, a larger-than-anticipated proportion of the opiate group had completed formal education post-high school. In fact, two thirds of both groups reported completing post-secondary school education in some capacity, and there was only a relatively small percentage difference between controls and opiate users who obtained college educations, 31 versus 23 %, respectively. It therefore seems likely that the sample obtained in this study is a higher-functioning subset of a vulnerable population, for whom cognitive functioning is largely intact. It is possible that for other, more impaired members of this population, significant correlations between executive control and episodic foresight may be evident. This is a possibility that warrants direct empirical investigation. Nevertheless, the present study's findings of only relatively limited executive difficulties in this population—coupled with significant deficits in episodic foresight—indicate that problems with episodic foresight are not simply secondary to more general control difficulties and may be a relatively pervasive feature of chronic opiate use that is evident even in relatively high-functioning sectors of this population.

In line with previous investigations of long-term substance use, a limitation of these data is the heterogeneity of substance use history among participants. It is unlikely that opiates are the drug of preference for novice users; therefore, opiate users inevitably have a long-running history of polydrug abuse and/or dependence. Moreover, the sample recruited in this study was participating in opiate substitution treatment. Thus, it is difficult to delineate the effects of opiates from other substances. Furthermore, we did not explore the influence of narrative ability (Brown et al. 2014; Gaesser et al. 2011) in explaining the pattern of results, which should be addressed in future studies.

In conclusion, although more work is required to understand why episodic foresight is compromised in this population, the results pave the way for further exploration of the underlying cognitive and neural mechanisms that may explain the observed impairments in the context of chronic opiate use, as well as other drug-using groups that exhibit similar, or even more severe, neurological impairments. Finally, these data provide valuable information that extends our understanding about the neurocognitive capacity of this clinical group, with potentially important implications for the refinement of current therapeutic interventions that incorporate the need to engage in future time projection.

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CHAPTER 6: Introduction to Article 2

6.1 Title

Exploring episodic foresight deficits in long term opiate users

6.2 Objective

Episodic foresight is a complex cognitive process. Although the relationship between episodic foresight and episodic memory has been consistently supported in the literature (Addis et al., 2007; Okuda et al., 2003; Szpunar et al., 2007) clinical groups have demonstrated specific impairments in episodic foresight which are not secondary to episodic memory deficits (de Vito et al., 2012; Irish et al., 2012; Mercuri et al., 2014). As a result, the literature has begun to investigate the influences of other contributing factors including scene construction and self-projection.

Scene construction refers to the ability to generate mental scenarios in one's mind irrespective of temporal context, whereas self-projection refers to the capacity to shift between alternative perspectives; for instance, different time periods. There is evidence to support the possible contribution of scene construction and self-projection to the impairment in episodic foresight deficit observed in chronic opiate users. Episodic foresight deficits identified in other clinical groups who have demonstrated similar patterns of impairment as observed in chronic opiate users, have been attributed to either scene-construction or self-projection deficits. Therefore the primary aim of the second study was to investigate whether deficits in scene construction and self-projection might underpin the compromised ability to mentally project the self into the future displayed by long-term opiate users.

6.3 Method

A modification of the adapted Autobiographical Interview (AI) used in the preceding study was administered to 35 long-term opiate users currently enrolled in an opiate

substitution treatment and 35 demographically matched controls. A portion of this sample was recruited from Study 1.

In this study the modified AI did not include the recall component. Rather, it included the original future condition (to assess self-projection) and two other imagination conditions (to assess narrative ability and scene construction). Interview transcripts were scored using the same procedures followed in the preceding study.

6.4 Results

The initial between-groups analysis revealed that the opiate user group performed significantly worse than the control group on the narrative task that required describing a story based on a predefined structure, as well as on the imagination task that required imagining the future. This initial finding suggested that impairments in episodic foresight may be underpinned simply by poor narrative ability. However to further explore this result, two within-group analyses were conducted to examine the how each experimental group performed across the three imagination conditions. These data highlighted that both groups performed better on the narrative task than either the scene construction and self-projection tasks. However, the opiate user group performed significantly worse when asked to engage in describing the future event than when instructed to engage in describing an atemporal event. This was not the case for the control group who performed comparably across the two conditions. These data suggest that a specific inability to mentally project the self into the future (which requires the capacity for self-projection) may underlie the episodic foresight deficit identified in chronic opiate users.

6.5 Conclusions

Given the extremely high rates of relapse reported in this clinical group, the findings of this study reinforce the importance of reassessing current relapse prevention protocols that

particularly rely on the client's capacity to project themselves into novel future scenarios.

This study proposes that relapse prevention should focus on achieving short-term, rather than long-term, treatment goals in order to reduce the demand for self-projection into unfamiliar future scenarios.

CHAPTER 7: Article 2

Deconstructing the nature of episodic foresight deficits associated with chronic opiate use.

Current status: Under review by *Drug and Alcohol Dependence*

Submitted for review on the 30th November, 2014

Appendices

Appendix B: Participant Recruitment and Informed Consent

Appendix C: Background Measures

Appendix E: Hospital Anxiety and Depression Scale

Appendix G: Modified Interview Script

Appendix H – 2: Confirmation of Submission for Article 2

Tables

Table 1 *Background characteristics of the control and opiate-user groups*

Table 2 *Details of the three scenarios in the imagination task*

Table 3 *Independent samples t-tests between control and opiate-user groups, comparing detail types in each interview condition*

Table 4 *Paired samples t-tests for each comparing performance across interview conditions for each detail type*

Figures

Figure 1. Mean number of internal and external details generated on the interview task as a function of group status (control group, $n = 35$; opiate-user group, $n = 35$) and imagination task condition. (Error bars depict standard error of the mean)

Abstract

Episodic foresight refers to the capacity to mentally travel forward in time, and has been linked to a wide variety of important functional behaviours. Evidence has recently emerged that chronic opiate use is associated with deficits in this critical capacity, and that these difficulties are not simply a secondary consequence of broader cognitive dysfunction. The current study aimed to better understand the circumstances in which chronic opiate users might be expected to have problems with episodic foresight, by addressing whether deficits reflect compromised scene construction, self-projection, or narrative ability. Thirty-five chronic opiate users and 35 demographically matched controls completed an imagination task in which they were instructed to imagine and provide descriptions of an atemporal event (to assess scene construction), a plausible, self-relevant future event (to additionally assess self-projection); as well as complete a narrative task (to test whether any difficulties simply reflect poor narrative ability). Consistent with prior literature, chronic opiate users exhibited reduced capacity for episodic foresight relative to controls. However, the present study was the first to show that these difficulties were independent of capacity for scene construction and narration. Instead, a specific impairment in self-projection appears to contribute to the problems with episodic foresight seen in this clinical group. Deficits in self-projection may have important implications in therapeutic environments given that many relapse prevention strategies rely heavily on the ability to project oneself into an unfamiliar future, free of problem substance use.

Keywords: Episodic foresight, episodic future thinking, opiate users, Autobiographical Interview, scene construction, self-projection

Introduction

Chronic opiate use is associated with poor functional, social, and economic outcomes (Hser et al., 2009; Villeux et al., 2010) and relapse following rehabilitation is common (Smyth et al., 2010). A recent study of long-term opiate users identified impairment in this group on a key cognitive ability, episodic foresight (Mercuri et al., 2014), that may help explain these functional difficulties and high relapse rates. Episodic foresight refers to the ability to mentally project oneself into the future and pre-experience events (Atance and O'Neill, 2001). It is a uniquely human characteristic that has immense survival value as it allows for the construction, mental enactment, and evaluation of future scenarios before deciding on the course of action most likely to achieve desired outcomes (Addis et al., 2007; Hassabis and Maguire, 2009; Suddendorf and Corballis, 2007). Not surprisingly then, episodic foresight has been strongly linked to independent living and a wide variety of adaptive behaviors (Suddendorf and Henry, 2013). Indeed, the importance of episodic foresight for successful daily living is reinforced by observations that a number of clinical groups with known functional difficulties present with significant impairment in this capacity, including individuals with autism (Lind and Bowler, 2010; Terrett et al., 2013), schizophrenia (Raffard et al., 2010), Parkinson's disease (de Vito et al., 2012), medial temporal lobe (MTL) damage (Race et al., 2011), and hippocampal amnesia (Hassabis et al., 2007b).

In the context of chronic opiate use, it therefore seems likely that any reduction in the capacity for episodic foresight will also have important implications for functional outcomes. For instance, difficulties with episodic foresight may have an impact on a client's prospects of successful rehabilitation given that many relapse prevention protocols involve asking clients to imagine themselves in future situations of temptation and generate strategies to prevent future lapses into problem drug use. Thus, impairment in this ability may directly limit treatment success and consequently increase the likelihood of relapse. It is therefore

crucial that we develop a clearer picture of the nature of this deficit, including addressing the key question of whether all, or only specific aspects of episodic foresight are disrupted in long-term opiate users. Developing a more nuanced understanding of when and why this complex cognitive capacity is likely to break down will allow for the provision of more effective support for daily living and more tailored rehabilitation services.

According to the *constructive episodic simulation hypothesis*, episodic foresight is a constructive process that involves two main phases. The first is a *construction phase* in which the simulation of personally relevant future events relies heavily on the retrieval of personally relevant memories of the past (episodic memory) to provide the basic building blocks for the construction of novel future scenarios (Schacter et al., 2007). The second phase involves inhibiting the tendency to simply retrieve actual memories and requires that the retrieved information be held in mind and flexibly manipulated so that past details are recombined into novel future events (Schacter and Addis, 2007). Referred to as the *elaboration phase* (Addis et al., 2007), this secondary process of recombining past information into a novel future experience is critical as it allows for the simulation of alternative scenarios without the need for behavioral engagement (Schacter and Addis, 2009).

Clearly episodic foresight is a complex process and one which imposes demands on many different cognitive operations. While the role of episodic memory has traditionally attracted most attention (Addis et al., 2007; Okuda et al., 2003; Szpunar et al., 2007), other contributing cognitive processes have also been proposed including semantic memory (Irish et al., 2012) and executive functioning (D'Argembeau et al., 2010; de Vito et al., 2012). Others have pointed to the potential importance of scene construction, and self-projection (Hassabis et al., 2007a, Hassabis et al., 2007b), and in the present study we will assess whether deficits in these latter two abilities contribute to the episodic foresight difficulties previously identified in chronic opiate users (Mercuri et al., 2014).

Scene construction refers to the process of building an imagined scenario in our mind. Different from visual imagery, scene construction involves mentally generating and combining multiple elements (e.g. contextual details, sensory details, thoughts, people, and objects) to create a coherent, spatial representation of an imagined scene (Hassabis et al., 2007a; Hassabis et al., 2007b). According to Hassabis et al. (2007b) this ability underpins a number of mental processes including spatial navigation and imagining fictitious experiences as well as mental time travel in both temporal directions (past and future). It has also been suggested however that re-experiencing the past and pre-experiencing the future require the additional capacity of self-projection (Buckner and Carroll, 2006). This refers to the ability to shift between one's immediate environment and an alternative perspective, such as a different spatial, mental, (or in the case of time travel) temporal perspective, and for that alternative perspective to be self-referenced (Buckner and Carroll, 2006). A number of studies have attempted to disentangle the roles of scene construction and self-projection in episodic foresight in a number of groups who have established episodic foresight deficits (e.g. D'Argembeau et al., 2010; de Vito et al., 2012; Lind et al., 2014; Raffard et al., 2010; Rendell et al., 2012).

Only one study to date has investigated the capacity for episodic foresight in the context of chronic opiate use, and as noted, the results showed that the ability to mentally travel forward in time is disrupted (Mercuri et al., 2014). This finding aligns with neuroimaging evidence that has consistently shown chronic opiate use to be associated with abnormalities in temporal regions including the medial temporal lobe (MTL; Cheng et al., 2013; Fu et al., 2008; Liu et al., 2009; Wang et al., 2012), the neural regions that have been most strongly linked to episodic foresight (see Suddendorf and Henry, 2013 for review). In particular, it has been suggested that the hippocampus is especially involved in the binding of retrieved information for the construction of a mental scene (Hassabis and Maguire, 2009).

Consequently, abnormalities in this area might be expected to particularly disrupt the capacity for scene construction. However, at a cellular level chronic opiate use accelerates natural aging processes, with the MTL atrophy observed in chronic opiate users mimicking that of healthy older adults (Cheng et al., 2013). Given that episodic foresight deficits in the context of aging have been linked to a diminished ability to project the self into a novel spatiotemporal context (Rendell et al., 2012), it might instead be that impaired self-projection is the central mechanism underpinning poorer episodic foresight in chronic opiate-users. The current study will be the first to deconstruct whether difficulties in scene construction and/or self-projection contribute to the episodic foresight deficits that have been identified in this group.

As noted previously, a better understanding of the mechanisms responsible for episodic foresight difficulties in chronic opiate users has potentially important clinical implications. This is because, given the relapsing nature of substance dependence, treatment predominately focuses on the prevention of future substance use. While the episodic foresight difficulties identified by Mercuri et al. (2014) provide a rationale for the modification of treatment protocols that rely on future-oriented thinking, the extent and nature of the required modifications remain poorly delineated. The findings of the current study will therefore provide much needed direction for tailoring intervention strategies to further enhance initial treatment success and long-term prospects of rehabilitation.

Method

Participants

This study was approved by the Australian Catholic University ethics committee and conformed to the ethical standards set out in the 1964 Declaration of Helsinki. Thirty-five long-term opiate-users (duration of opiate use: $M = 15.15$ years, $SD = 9.97$), aged between 27 and 61 years were recruited. The control group consisted of 35 adults aged between 20 and 56

years with no reported history of alcohol or other drug dependence¹. The two groups did not differ significantly on gender, $\chi^2(1, 70) = 2.20, p = 0.138$, and as can be seen in Table 1, were closely matched on age as well as premorbid IQ as measured by the National Adult Reading Test (Nelson, 1982). However the opiate group had fewer years of formal education, and reported greater negative affect as measured by total scores on the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983). The participants in the opiate-user group were currently enrolled in an opiate substitution program (Methadone $n = 24$ and Suboxone $n = 11$), with the average dose of Methadone received daily 61.60mg ($SD = 38.59$) and Suboxone, 11.14mg ($SD = 9.09$). Frequencies of participants reporting current substance use are displayed in Table 1.

Most participants were recruited through a database of individuals who had previously participated in projects conducted by our research team. The remaining participants in the control group were recruited through the researcher's social networks, and the opiate group from fliers distributed through pharmacies that dispensed opiate substitution treatments. Eligibility was determined by fulfilment of the same inclusion criteria used by Mercuri et al. (2014). All participants were reimbursed up to AU\$30 (~USD\$30) for their time.

¹ Eight-two percent of the opiate group and 97% of the control group participants were recruited from Study 1. Independent samples t-tests comparing the interview performance between the re-recruited and new participants were conducted for each experimental group separately. Results did not reveal any significant differences with all $ps > .411$ for the opiate group and all $ps > .114$ for the control group.

Table 1

Background characteristics of the control and opiate-user groups

	Control Group <i>n</i> = 35 ^a		Opiate Group <i>n</i> = 35 ^b		<i>t</i> (68)	<i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Proportion of Men (%)	54%		71%			
Age (in years)	36.00	10.85	40.37	9.17	1.82	0.44
Education (in years)	14.26	2.67	12.56	2.34	2.75*	0.69
Estimated IQ	110.19	7.41	111.81	4.88	1.08	0.26
<i>Mental Health</i>						
Depression	2.83	2.77	7.50	4.34	5.35***	1.31
Anxiety	5.71	3.71	9.32	4.81	3.50**	0.86
Frequency of participants engaging in current substance use						
Nicotine users (No:Yes) ^c	26:9		8:27			
Alcohol (No:Yes) ^d	5:30		17:18			
Cannabis (No:Yes) ^e	29:6		15:20			
Amphetamines (No:Yes) ^f	26:9		31:5			
Cocaine (No:Yes) ^g	34:1		34:1			
Benzodiazepines (No:Yes)	35:0		25:10			
Heroin (No:Yes) ^h	35:0		18:17			

^a all *ns* = 35 except 'Education' where *n* = 34^b all *ns* = 35 except years of 'Education' where *n* = 32 and 'Mental health' where *n* = 34^c daily frequency of nicotine use reported for both groups^d weekly frequency of alcohol use reported for both groups^e 4/6 control group users reported *monthly or less* frequency, 16/20 of opiate group users reported '*at least once a week*' frequency^f *less than once a month* frequency reported by both groups^h 12/17 opiate group reported *weekly* use* *p* < 0.05, ** *p* < 0.01, *** *p* < 0.001

Materials

Imagination task

Episodic foresight was assessed using a modification of Addis et al. (2007) Adapted Autobiographical Interview (AI). The AI is a semi-structured interview used to assess episodic and non-episodic content in two temporal phase conditions (past and future). Because the focus here is episodic foresight, the current study only administered the future condition. To further deconstruct episodic foresight ability the interview was manipulated by incorporating two other imagination conditions (atemporal and narrative) developed by

Hassabis et al. (2007b). In the original protocol, Hassabis et al. (2007a) provided participants with ten verbal cues and asked them to imagine and provide descriptions of an atemporal event (to assess scene construction), a plausible, self-relevant future event (to additionally assess self-projection), as well as complete a narrative task (to provide participants with a story structure on which to base their description of an event). The narrative task makes the lowest demands on imagination and therefore provides an important means of testing whether any difficulties on this interview-format task simply reflect poor narrative ability. Although all three conditions provide some measure of scene construction related to imagination, the variations between the three tasks allow the disentangling of which abilities might be specifically compromised. For instance, the future condition is the only task that involves a temporal element, and therefore difficulties on this task in comparison to the other two suggest that episodic foresight deficits reflect particular problems specifically with the self-projection component of this process.

Testing sessions: Participants were informed that the task would involve separately imagining three different scenarios (future, atemporal, and narrative; see Table 2 for descriptions). Participants were instructed to imagine each scenario as vividly as possible and then describe it aloud in as much detail as possible, while being recorded on a digital voice recorder. Participants were told to give free rein to their imagination and to describe the experience or event using all available senses including what they could see, hear, smell, and feel. Specific to the future condition, it was made clear that the task was designed to assess how participants' visualize and imagine, so participants were instructed not to use an existing memory but to create a new scene. Three minutes were allocated for each response. As soon as the researcher provided the task description, participants were given time to think about a response and once they indicated that they were ready, timing began. Before commencing, the researcher demonstrated the task using an example: "*imagine you're sitting on a bench in*

a park". The experimenter read a prepared response as if they were making it up to provide a model of imagining a new scenario. The experimenter then checked the participant was clear about what was required.

Set prompts were provided when clarification of instructions or facilitation of further event description was required; for example, "Can you give me more details on X?". If it was suspected that a participant was only using superficial semantic statements, they were asked, "What does X look/sound/ smell like?". The protocol strictly prohibited the experimenter from introducing any concept, idea, detail, or entity that had not already been mentioned by the participant.

Table 2 displays the three scenario cues presented to participants, one each for the "future", "atemporal" and "narrative" condition. The future cue asked participants to imagine themselves within a particular scene in the future and describe it as if they were experiencing it at the present moment. The atemporal cue required imagining a scene with no temporal component included. The scene to be described was a commonplace setting, which minimizes the difficulty level and any reliance on innate creativity. The final scenario was the narrative condition which was similar to the atemporal condition in that it did not include any temporal instructions but differed by involving constructing a narrative where participants were given the additional instruction of moving through the scene (walking through a castle) to reach a specified goal (reach the tower at the top of the castle).

Table 2

Details of the three scenarios in the imagination task

Narrative scenario	<i>Imagine you are standing in the middle of the impressive high vaulted entrance hall of an old castle. There is a tower somewhere in the castle, the top of which is accessed via a circular winding staircase. I want you to describe to me in as much detail as possible your route through the castle's many rooms and floors until you reach the top of the tower. Use all your senses including what you see, feel, and do on the way to the tower.</i>
Atemporal scenario (scene construction)	<i>Imagine you are sitting having a drink in a café. I want you to describe the experience and the surroundings in as much detail as possible using all your senses including what you can see, hear, and feel.</i>
Future scenario (self-projection)	<i>Imagine something you could be doing next summer, but just give me one event. I want you to describe that event and the surroundings in as much detail as possible using all your senses including what you can see, hear, and feel.</i>

Scoring: For each transcribed scenario description, details were segmented and categorized as either internal (episodic details specific to the central event) or external (non-episodic details including: repetitions, semantic information, and information not specific to the central event). The number of internal details within each condition provided an index of the extent to which participants were personally experiencing the event in their imagination. Two independent scorers who were blind to project aims and participant group membership scored the transcripts. Training manuals were provided by Donna Addis, which included an annotated example of scoring and twenty scoring events. Inter-rater reliability between the two scorers and the scoring events provided in this manual was assessed on the basis of a two-way mixed-design Analysis of Variance (ANOVA) intraclass correlation analysis. The Cronbach alphas obtained with our two scorers were 0.96 for internal details and 0.92 for external details. The three scorers coded portions of the full dataset and each scorer was assigned an equal number of transcripts from both experimental groups.

Results

The first step in this analysis involved assessing any potential differences in the amount of verbal output by the opiate and control group in order to ensure that any observed differences in the number of internal details generated by the two groups were not simply a reflection of differences in overall verbal output. An independent samples *t*-test found no significant differences ($p = 0.169$) between the opiate ($M = 222.42$, $SD = 100.92$) and control groups ($M = 257.12$, $SD = 107.54$) in the total number of details generated across all three interview conditions, suggesting no differences in overall amount of verbal output. Separate *t*-tests were also conducted for each imagination condition and revealed no differences in the total number of details generated in each of the narrative ($p = 0.075$), scene construction ($p = 0.430$), and self-projection ($p = 0.339$) conditions, between the opiate ($M = 79.37$, $M = 72.14$, $M = 74.57$, respectively) and control groups ($M = 97.37$, $M = 79.37$, $M = 83.15$, respectively).

The next step in the analysis involved investigating the number of details generated in each of the imagination tasks for the two groups. These data were analysed using a mixed 2 x 3 x 2 ANOVA where the between-groups variable was *group status* (opiate user group, control), the within-groups variables were *condition* (narrative, atemporal, future) and *type of details* (internal, external), and the dependent variable was the number of details generated². These data are shown in Fig. 1.

² Given the higher levels of negative affect reported in the opiate group, it was important to consider whether mental health issues may have had an impact on episodic foresight ability. No significant associations were evident between the outcome variable of internal details with either depression or anxiety for both the control (all $ps \geq 0.246$) and opiate-user group (all $ps \geq 0.110$). Consequently, no statistical control for these variables was required for the ANOVA analysis (Tabachnick & Fidell, 2006). Using multivariate statistics. Pearson, Boston.

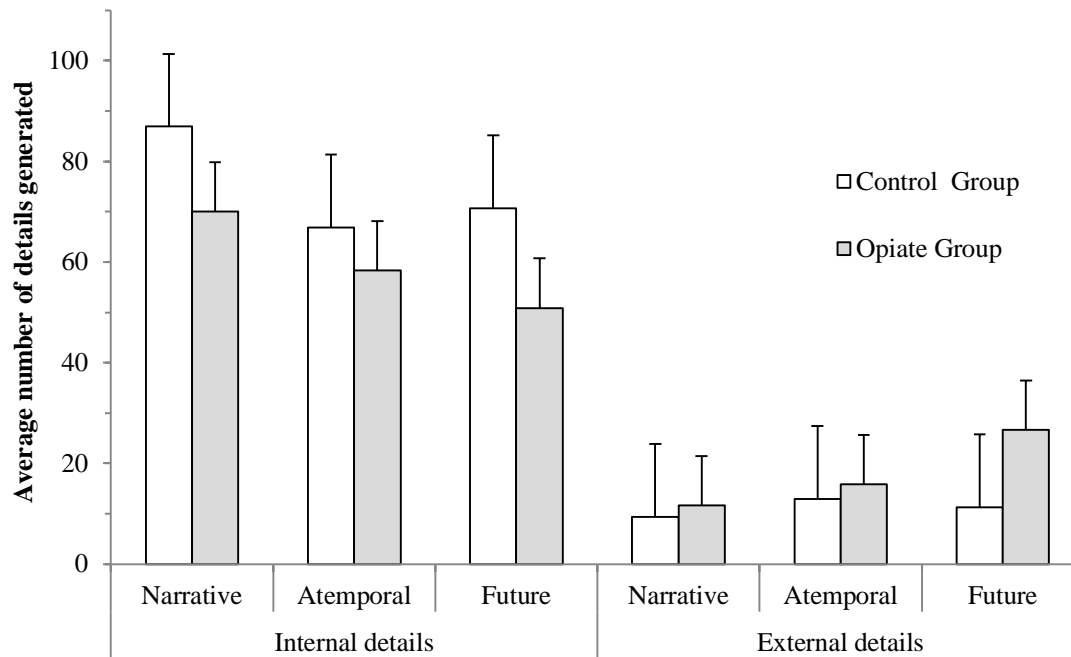


Figure 1. *Mean number of internal and external details generated on the interview task as a function of group status (control group, $n = 35$; opiate-user group, $n = 35$) and imagination task condition. (Error bars depict standard error of the mean)*

The results identified main effects of condition, $F(2, 68) = 9.66, p < 0.001, \eta_p^2 = 0.12$, and detail type $F(2, 67) = 167.86, p < 0.001, \eta_p^2 = 0.71$, power = 0.98, indicating that overall participants provided more details in the narrative condition ($M = 43.57, SD = 2.4$), than the atemporal ($M = 37.88, SD = 2.3$) and the future ($M = 38.44, SD = 2.02$) conditions, and produced more internal than external details. However there was no main effect of group status $F(1, 67) = 1.94, p = 0.169, \eta_p^2 = 0.03$, power = 0.279. The two-way interaction of condition and group status was also not significant, $F(2, 67) = 2.10, p = 0.126, \eta_p^2 = .03$, power = 0.425 but the other two way interactions were: condition and detail type, $F(1, 136) = 19.26, p < 0.001, \eta_p^2 = 0.22$, power = 1.000 and group status and detail type, $F(1, 68) = 7.59, p < 0.010, \eta_p^2 = 0.71$, power = 0.775. However, superseding these main and two-way interaction effects was the finding of a three way interaction,

$F(2, 136) = 3.82, p = 0.024, \eta_p^2 = 0.05$, power = 0.686. As group status and condition were the two variables of interest, this was followed up by analysing the results for group and condition separately for internal and external details.

Analysis of group differences for each imagination condition for each detail type

Independent samples *t*-tests comparing the two groups on each interview condition showed that, relative to the control group, opiate users were poorer at generating internal details in the narrative ($p = 0.042$) and future ($p = 0.009$) conditions, but not the atemporal ($p = 0.258$) condition (see Table 3). For external details, the opiate group produced more external details than the control group in all three imagination conditions (see Table 3).

Table 3

Independent samples *t*-tests between control and opiate-user groups, comparing detail types in each interview condition

	Control Group <i>n</i> = 35		Opiate Group <i>n</i> = 35				
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i> (68)	<i>d</i>	Power
Narrative							
Internal details	86.89	41.27	70.00	39.74	1.77*	0.50	0.42
External details	9.35	6.83	10.45	9.12	0.57	0.16	0.08
Atemporal							
Internal details	66.89	34.63	58.31	34.17	1.05	0.25	0.18
External details	11.77	10.32	14.36	13.34	0.92	0.22	0.15
Future							
Internal details	70.64	37.68	50.85	33.00	2.35*	0.56	0.65
External details	10.87	8.20	23.33	19.82	3.45**	0.76	0.93

* $p < .05$, ** $p < .01$, *** $p < 0.001$

Analysis of imagination condition differences for each group for each detail type

Paired samples *t*-tests were conducted to compare the number of details generated across the interview conditions within each group. These data are reported in Table 4, separately for each detail type. In relation to internal details, the control group produced more details in the narrative condition compared to both the atemporal and future scenarios. However, no difference in performance was found when comparing the atemporal and future tasks. By contrast, the opiate group generated fewer details in the future condition when compared to both the narrative and atemporal tasks. However no difference was found when comparing the narrative and atemporal conditions (see Table 4). Analysis of external details revealed different patterns of performance across the conditions for each group. The control group's performance was comparable across the three interview conditions. However the pattern for the opiate group was in contrast to that for their internal details, with more external details produced in the future condition than in the atemporal and narrative tasks.

Table 4

Paired samples t-tests for each comparing performance across interview conditions for each detail type

	Control Group		Opiate Group	
	<i>n</i> = 35		<i>n</i> = 35	
	<i>t</i> (34)	<i>d</i>	<i>t</i> (34)	<i>d</i>
Internal details				
Narrative vs. Atemporal	4.33 ^{***}	0.73	1.94	0.33
Narrative vs. Future	3.70 ^{**}	0.63	3.51 ^{**}	0.60
Atemporal vs. Future	0.88	0.15	2.20 [*]	0.38
External details				
Narrative vs. Atemporal	1.23	0.21	1.87	0.32
Narrative vs. Future	0.93	0.16	4.08 ^{***}	0.69
Atemporal vs. Future	0.58	0.10	3.47 ^{**}	0.58

* $p < .05$, ** $p < .01$, *** $p < 0.001$

Discussion

In the present study chronic opiate users were found to generate significantly fewer episodic details when imagining a novel future scenario, which aligns with the only prior study to investigate episodic foresight in chronic opiate users (Mercuri et al. 2014). However these data extend previous work by providing key insights into the mechanisms underlying episodic foresight difficulties in chronic opiate users. In particular, because the two groups were found to differ in their capacity to imagine a personal event in the future - but not in their ability to construct an atemporal mental scenario - this suggests that the episodic foresight difficulties associated with chronic opiate use do not reflect difficulties with scene construction, but instead suggest difficulties with the self-projection component of this

process. Analysis of the pattern of results for the opiate user group across the conditions further supported this possibility, as fewer episodic details were generated when imagining the future scenario compared to constructing an atemporal scene. Furthermore, the fact that this group produced most non-episodic responses on the task that required the ability to mentally project the self into a novel future scenario is consistent with the notion that they found this task the most cognitively challenging (Arnold et al., 2011; D'Argembeau et al., 2010). By contrast, there was no difference in the control group's performance across these two conditions, suggesting that they did not find the task requiring the construction of a future scene with its additional requirement for self-projection any more challenging than constructing an atemporal scene.

Despite the fewer episodic details generated in the narrative condition by the opiate group relative to the control participants, both groups performed better in the narrative condition compared to when constructing a future scenario. As a result, deficits in the capacity for mental construction of novel future experience do not appear to be secondary to impoverished narrative ability. The poorer capacity for narrative construction may be explained by variables more closely linked to linguistic ability, and therefore should be explored further.

Taken together, these data therefore provide novel evidence that the episodic foresight difficulties associated with chronic opiate use are independent of scene construction and narrative ability. Instead, the most parsimonious explanation is that difficulties adopting alternative perspectives related to the self in a future temporal context contribute to reduced episodic foresight in this group. Interestingly, reduced capacity for self-projection was also implicated in the decline in episodic foresight amongst older adults identified by Rendell et al. (2012) raising the possibility that there may be some overlap in areas of brain impairment, possibly in the MTL, between these two groups.

Overall, these findings are important, not only theoretically, but also in terms of their potential practical implications for improving independent living. Indeed, D'Argembeau et al. (2011) highlighted the prominent role that thinking about the future plays in everyday life, reporting that in healthy adults the frequency of future-oriented thoughts outweighs those about the past, with a future thought occurring every 16 minutes. In fact, this study showed that individuals tend to simulate hypothetical future outcomes when engaging in processes such as planning, decision-making, problem solving, and other goal-related cognitions essential for successful daily functioning. It therefore seems likely that any problems with episodic foresight may contribute to the functional difficulties associated with chronic opiate use. Consequently, in order to better support functional capacity in this group, it may be valuable to modify interventions in rehabilitation settings so that clients are taught strategies to evaluate possible courses of action that are less reliant on the need to personally imagine the self-experiencing the future. In this way, any potential impact of this cognitive limitation may be minimized.

This is a possibility that warrants serious further empirical study, particularly given the very high rate of relapse often seen in opiate users (McLellan et al., 2000). Indeed, one recent study reported a relapse rate of 91% in this cohort within one year of inpatient treatment (Smyth et al., 2010). Treatment of substance dependence therefore relies heavily on relapse prevention, which often involves a focus on developing skills to confidently reject future drug offers, formulation of methods for managing exposure to relapse triggers, and cost-benefit analysis of changing current drug-related behaviors. Problems engaging in episodic foresight may help explain why these individuals experience difficulties achieving and maintaining abstinence. More specifically, our results suggest that while substance dependent individuals may be able to imagine and construct a mental image of a substance free existence in the present moment, they have difficulty in mentally projecting this scenario

into a future time period. Such findings point to the potential value of constructing short-term treatment objectives, rather than planning goals that are in the client's distant future. Relapse prevention strategies may therefore have better success if they focus on the client's current needs and assist the client in fulfilling immediate treatment related goals such as remembering to collect pharmacotherapy, presenting to mandatory medical appointments in order to refill prescriptions, and attending therapy.

In conclusion, the present study identifies for the first time one of the underlying mechanisms that contributes to the episodic foresight difficulties seen in chronic opiate users. Specifically, these data provide evidence for a specific problem implementing the self-projection component of this process. These data provide a platform for future studies that use neuroimaging procedures to explore the neural underpinnings of these deficits. The results also have potentially important implications for refinement of rehabilitation programs, providing guidance for how treatment protocols might be tailored to more strongly align with the cognitive abilities of chronic opiate users (as well as potentially other substance abuse groups that may exhibit a qualitatively similar profile of deficits).

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CHAPTER 8: Introduction to Article 3

8.1 Objective

Although chronic opiate use is associated with greater deleterious outcomes, cannabis continues to be the most widely used substance worldwide and there is an increasing demand for cannabis-related treatment (United Nations Office of Drugs and Crime, 2014). Cannabis is derived from the Cannabis Sativa plant and its psychoactive effects are attributed to the cannabinoid known as delta-tetrahydrocannabinol (THC). THC binds to type – 1 cannabinoid (CB1) receptors found in a number of prefrontal and temporal brain structures (Ameri, 1999; Pertwee, 2008). Not surprisingly a number of studies have identified cannabis-related declines in executive processing, learning, and memory (Abdullaev et al., 2010; Bolla et al., 2005; Curran et al., 2002; Solowij et al., 2002).

Given these identified impairments the question of interest in Study 3 was whether episodic foresight deficits might be found in other, arguably less harmful, drugs such as cannabis. Thus the primary aim of this third study was to directly assess episodic foresight ability in the context of regular cannabis use. The secondary was to examine whether episodic memory and executive control would contribute to episodic foresight within the context of regular cannabis use.

8.2 Method

This third study administered the same protocol used in Study 1. Episodic foresight was assessed using the Adapted Autobiographical Interview. Three measures of executive functioning were also administered to 25 regular cannabis users and 45 demographically matched substance naïve controls. Both groups were recruited through the Australian Catholic University and the researcher's social network.

8.3 Results

The results did not reveal cannabis-related deficits in episodic foresight, episodic memory, or executive control. However significant relationships between episodic foresight and episodic memory, and between episodic foresight and executive functioning were observed in both experimental groups, which provided some support for the constructive episodic simulation hypothesis.

8.4 Conclusions

This study is the first to directly assess episodic foresight ability in the context of cannabis use. The findings provide support for the involvement of memory and executive processes in the capacity for episodic foresight, but did not identify cannabis-related deficits. The results therefore suggest that episodic foresight ability is spared in this cannabis-using sample, although a number of suggestions are explored to explain this absence of impairment.

CHAPTER 9: Article 3

Episodic foresight in regular cannabis users

Current status: Submitted for review to the *Journal of Clinical and Experimental Neuropsychology* on 4th January, 2015

Appendix B: Participant Recruitment and Informed Consent

Appendix C: Background Measures

Appendix D: Adapted Autobiographical Interview Script

Appendix H – 3: Confirmation of Submission for Article 3

Tables

Table 1 *Participant characteristics*

Figures

Figure 1. *Mean number of internal and external details generated on the AI as a function of group status (substance naive control group, $n = 45$; cannabis user group, $n = 25$) and temporal direction. (Error bars depict standard error of the mean)*

Figure 2. *Mean number of internal and external details generated on the AI as a function of group status (substance naive control group, $n = 45$; cannabis user group, $n = 25$) (Error bars depict standard error of the mean)*

Figure 3. *Mean number of internal and external details generated on the AI as a function of temporal direction (past, future) (Error bars depict standard error of the mean)*

Abstract

There is considerable literature showing that cannabis use is associated with a range of neurocognitive deficits, including deficits in executive control and episodic memory. However, no study to date has assessed whether these neurocognitive difficulties extend to the ability to mentally time travel into one's personal future. This is a surprising omission given that executive control and episodic memory are considered to be critical to engage episodic foresight. Therefore, in the present study we assessed how episodic foresight is affected in the context of regular cannabis use, and examined the degree to which performance on a measure of episodic foresight is correlated with performance on measures of episodic memory and executive control. Twenty-five regular cannabis users and 45 substance naive controls were assessed using three measures of executive function and an adapted version of the Autobiographical Interview as an index of episodic foresight and episodic memory. The results provide no evidence of cannabis-related impairment in episodic foresight, episodic memory, or executive functioning. However it is possible that this lack of episodic foresight deficit may be attributable to factors related to the nature of the cannabis use and/or to compensatory cognitive mechanisms. The present study indicates that cannabis use may not always disrupt cognitive function, and shows for the first time that this extends to the capacity for episodic foresight.

Keywords: Episodic foresight, cannabis, Autobiographical Interview, executive functions, episodic memory

Introduction

The primary ingredient responsible for the psychoactive effects of cannabis is Δ^9 – tetrahydrocannabinol (THC; Pertwee, 2008). THC binds to Type 1 cannabinoid (CB1) receptors, high densities of which are found in frontal and temporal brain regions (Ameri, 1999; Glass, Dragunow, & Faull, 1997; Mechoulam & Parker, 2013; Quickfall & Crockford, 2006). THC appears to contribute to many of the cognitive effects of cannabis use, including reduced capacity for executive control, learning, and memory (Abdullaev, Posner, Nunnally, & Dishion, 2010; Bolla, Elderth, Matochik, & Cadet, 2005; Curran, Brignell, Fletcher, Middleton, & Henry, 2002; Ilan, Smith, & Gevins, 2004; Solowij et al., 2002).

Episodic foresight is a critically important cognitive ability which refers to the capacity to mentally travel forward in time. Importantly, evidence now indicates that the ability to apply episodic foresight relies on a range of cognitive skills, including many of those affected by cannabis use, such as episodic memory and executive control (Schacter & Addis, 2007). More specifically, according to the *constructive episodic simulation hypothesis*, past episodic memories are required to provide the building blocks for the mental construction of hypothetical future events, and executive processes assist in the flexible recombination of these memories into a new time period to avoid simply recasting the past memories (Schacter & Addis, 2007; Suddendorf & Henry, 2013). It is therefore a surprising omission in this literature that no study to date has directly assessed whether the capacity for episodic foresight is disrupted in the context of cannabis use.

In addition to theoretical value, such an assessment has potentially important practical implications. This is because episodic foresight has been consistently linked to independent living and a wide variety of functional behaviors (Suddendorf & Henry, 2013). Given that regular cannabis use is associated with a number of psychosocial deficits (see Hall, 2014 for review), it is important to clarify whether a breakdown in episodic foresight potentially

contributes to these difficulties. Consistent with such a possibility, deficits in episodic foresight have been consistently identified in other clinical groups that present with reduced functional capacity (de Vito et al., 2012; Hassabis, Kumaran, Vaan, & Maguire, 2007; Irish, Addington, Hodges, & Piguet, 2012; Lind, Williams, Bowler, & Peel, 2014; Race, Keane, & Verfaellie, 2011; Raffard, D'Argembeau, Bayyard, Boulenger, & van der Linden, 2010; Terrett et al., 2013), including chronic opiate users (Mercuri et al., 2014).

Amongst this research, Mercuri et al.'s (2014) study with opiate users is the only one to date to investigate episodic foresight in the context of substance misuse. Consequently, the present study aimed to address an important gap in the literature and clarify for the first time whether regular use of cannabis also disrupts capacity for episodic foresight. Because of evidence showing that this drug particularly affects a number of the neural regions known to be implicated in episodic foresight, and disrupts many of the cognitive operations believed to be involved in this capacity such as executive control and memory, we anticipated that regular cannabis use would be associated with difficulties applying episodic foresight. Our secondary question was to clarify the degree to which episodic foresight performance in regular users of cannabis is correlated with performance on measures of episodic memory and executive control.

Method

Participants

This study was approved by the Australian Catholic University ethics committee and conformed to the ethical standards set out in the 1964 Declaration of Helsinki. Twenty-five regular cannabis users aged 18 to 30 years were recruited, as well as 45 controls aged 18 to 29 years with no history of illicit drug use. All participants were recruited using a range of

community advertisements, and social networking³. Although 33 cannabis users initially responded, eight participants were excluded due to relatively infrequent use or an absence of current cannabis use. Exclusion criteria for both groups included: a previous or current neurological condition; a psychiatric disorder; a history of heavy alcohol use (defined as 28 standard drinks per week for men and 14 for women) (Australian National Health and Medical Research Council, 2001); or a previous acquired brain injury. Participants were instructed to refrain from use of alcohol or illicit drugs in the 24 hours prior to testing. Participants were sent a reminder text message at least 24 hours prior to their testing time and abstinence was confirmed via self report on the day of testing. Participants were also excluded if English was not their first language. All participants were reimbursed up to AU\$30 (~USD\$30) for their time.

The cannabis sample consisted of relatively novice, but regular users of the drug. Seventy-two percent of the total cannabis sample reported “*at least fortnightly*” frequency of use and the remaining reported “*at least monthly*”. Over two thirds (68%) described dosage of use per sitting as “*one to three joints*” with the remaining participants reporting “*three or more joints*”. Forty-four percent of the sample categorized their duration of use as “*between six and twelve months*”, 36% reported “*1 – 5 years*” of use, and the remaining 20% reported “*at least 5 years*” of cannabis use. Although duration of use (in years) was reported categorically, age of onset was approximated by subtracting the lower bound of the duration category from the participant’s age. The average age of onset was relatively high ($M = 19.34$ years, $SD = 2.35$). Frequencies of current alcohol and other drug use for the cannabis group are displayed in Table 1.

³ This sample did not include any participants from the previous studies conducted by the researchers investigating episodic foresight in long-term opiate use.

Table 1

Participant Characteristics

	Substance naïve control group <i>n</i> = 45	Cannabis user group <i>n</i> = 25		
Proportion of Men (%)	15%	36%		
	<i>M</i> ± <i>SD</i>	<i>M</i> ± <i>SD</i>	<i>t</i> (68)	<i>d</i>
Age (in years)	20.91 ± 2.81	21.04 ± 3.19	0.17	0.04
Education (in years)	15.30 ± 14.41	14.32 ± 0.97	2.60**	0.63
Estimated IQ	110.08 ± 4.80	111.07 ± 4.82	0.82	0.20
<i>Psychopathology</i>				
Depression ^a	2.20 ± 2.13	4.00 ± 3.93	2.10*	0.51
Anxiety ^a	6.61 ± 2.58	6.28 ± 4.54	0.33	0.80
<i>Executive Functions</i>				
Verbal Fluency	57.58 ± 17.04	63.56 ± 14.20	1.57	0.38
Cognitive Flexibility	28.32 ± 14.75	32.14 ± 17.13	0.94	0.23
Inhibition	6.29 ± 0.83	6.40 ± 0.54	0.25	0.06
	<i>n</i> (No: Yes)	<i>n</i> (No: Yes)		
Alcohol ^b users (No:Yes)	0:45	0:25		
Amphetamine users (No:Yes)	-	10:15 ^c		
Cocaine users (No:Yes)	-	18:7 ^c		
Heroin users (No:Yes)		25:0		
Hallucinogen users (No:Yes)	-	20:5 ^c		
Benzodiazepine users (No:Yes)	-	22:3 ^c		

d = Cohen's *d* index of effect size. Cohen (1999) defines effect sizes of 0.2 as small, 0.5 as medium, and 0.8 as large.

^a *df* adjusted for unequal variances

^b *weekly* frequency of use for both groups

^c *monthly or less* frequency of use

* *p* < .05, ** *p* < .01, *** *p* < 0.001

As shown in Table 1, although the groups differed on years of formal education, they were matched on age and premorbid intelligence as measured by the National Adult Reading Test (Nelson, 1982), and did not significantly differ in gender, $\chi^2(1, 70) = 3.81, p = .051$. The

cannabis group did however report higher levels of depressive symptoms, but not anxiety, as measured by the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983).

Materials

Executive control

Three measures which are particularly sensitive to mental flexibility, inhibitory control, and cognitive initiation were used as indices of executive control. Mental flexibility was assessed using the Trail Making Test (TMT), the Hayling Sentence Completion Test was used to assess inhibitory control (Burgess & Shallice, 1997), and a verbal fluency (both phonemic and semantic probes) task was administered to assess cognitive initiation (Strauss, Sherman, & Spreen, 2006). For more details of the measures used, please see Mercuri et al. (2014).

Episodic foresight and episodic memory

Episodic foresight and episodic memory were assessed using the Addis, Wong, and Schacter (2008) adaptation of the Levine, Svoboda, Hay, Winocur, and Moscovitch (2002) Autobiographical Interview (AI). The AI is a semi-structured interview which provides an index of both episodic foresight and episodic memory by assessing episodic and non-episodic content in two temporal phase conditions (past and future). Participants are instructed to describe a personally experienced event from their past or a novel future event in response to a cue word. Six cue words used were chosen to prompt event descriptions. They were chosen from the “Affective Norms for English Words List” (ANEW; Bradley & Lang, 1999), and were the same as those used in the Mercuri et al. (2014) study. A maximum of three minutes was allocated for each description. Interview transcripts were independently scored by two trained scorers⁴, and scoring was based on the type of details generated by the participants.

⁴ Inter rater reliability between the three scorers was assessed on the basis of a two-way mixed-design Analysis of Variance (ANOVA) intraclass correlation analysis. The Cronbach alphas obtained with our three scorers was 0.90 for internal and 0.87 for external details.

Details were segmented and categorized as either internal (episodic details specific to the central event) or external (non-episodic details including: repetitions, semantic information, and information not specific to the central event). The number of internal details generated for future events is the primary measure of episodic future thinking and the number of internal details for past events indexes episodic memory. Further details relating to the administration and scoring of the AI can be found in Mercuri et al. (2014).

Procedure

All participants provided informed consent and were all tested individually in one session of approximately three hours duration, with breaks provided as needed.

Administration of cognitive assessments was counterbalanced.

Data Analysis

All statistical tests were 2-tailed. An alpha level of $p < 0.05$ was considered significant, and effect sizes were estimated using partial eta squared (η^2_p). Data were screened for missing values and outliers. Little's MCAR test indicated that data was missing completely at random, $\chi^2(1) = 7.84$, $p = 0.797$, therefore expectation maximization was used to replace missing values. Significant positive skewness was rectified using logarithmic transformations.

Results

Background measures of cognitive functioning

Descriptive and inferential statistics for the TMT, Hayling, and verbal fluency tests are reported in Table 1. It can be seen that there were no group differences on any of the executive function measures.

Autobiographical Interview (AI)

The first step in this analysis involved assessing any potential differences in the amount of verbal output by the cannabis and control group in order to ensure that any observed differences in the number of internal details generated by the two groups were not simply a reflection of differences in overall verbal output. An independent samples *t*-test found no significant differences ($p = .450$) between the cannabis ($M = 607.80$, $SD = 137.58$) and control groups ($M = 576.19$, $SD = 210.14$) in the total number of details generated across all three interview conditions, suggesting no overall differences in verbal output.

The next step in the analysis involved investigating the number of details generated for the past and future event descriptions for the two groups. These data were analyzed using a mixed 2 x 2 x 2 ANOVA where the between group variable was *group status* (cannabis user group, control), and the within group variables were *temporal direction* (past, future) and *detail type* (internal, external). These data are shown in Figure 1.

The independent variable of primary interest, group status, was not a main effect, $F(1, 68) = 0.46$, $p = .501$, $\eta_p^2 = 0.007$, power = 0.050 but did interact with detail type, $F(1, 68) = 5.67$, $p = .020$, $\eta_p^2 = 0.08$, power = 0.349. Group status did not interact with temporal direction, $F(1, 68) = 0.06$, $p = .804$, $\eta_p^2 < 0.01$, power = 0.191 and three way interaction was not significant, $F(1, 68) = 0.37$, $p = .544$, $\eta_p^2 < 0.01$, power = 0.200. The other two independent variables were main effects: temporal direction, $F(1, 68) = 101.93$, $p < .001$, $\eta_p^2 = 0.60$, power = 1.000, and detail type, $F(1, 68) = 172.94$, $p < .001$, $\eta_p^2 = 0.73$, power = 1.000. These main effects were trumped by the interaction of group status and detail type and the interaction of temporal direction and detail type, $F(1, 68) = 59.73$, $p < .001$, $\eta_p^2 = 0.47$, power = 1.000.

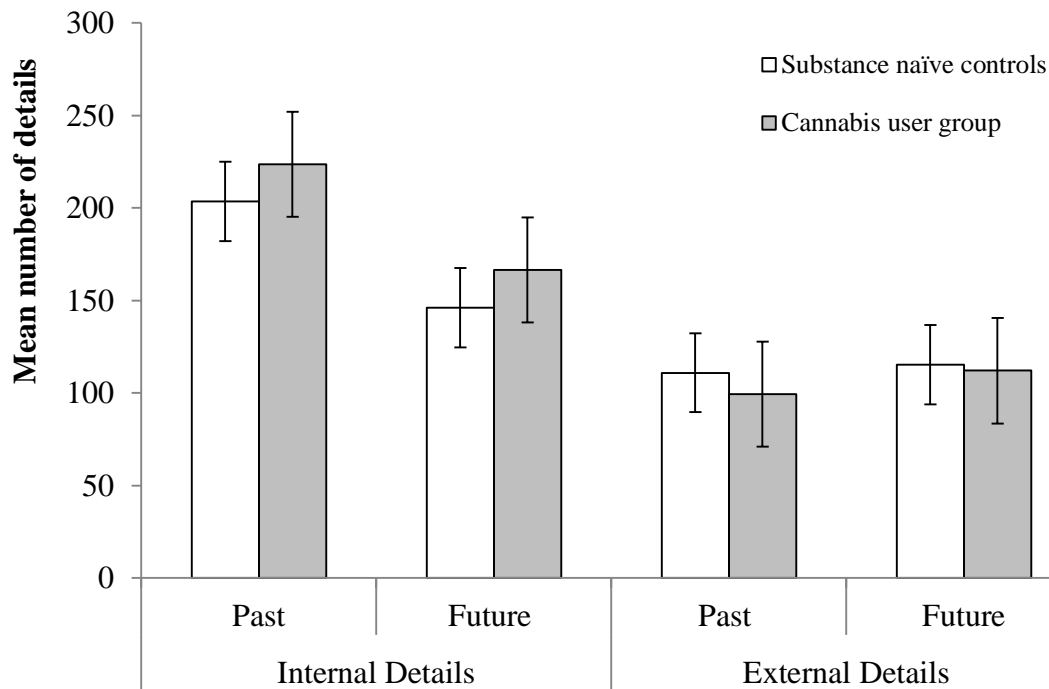


Figure 1. *Mean number of internal and external details generated on the AI as a function of group status (substance naïve control group, $n = 45$; cannabis user group, $n = 25$) and temporal direction. (Error bars depict standard error of the mean)*

For the interaction between detail type and group status, tests of simple effects revealed the group differences were not significant for both internal details, $F(1, 68) = 2.67$, $p = .107$, $\eta_p^2 = 0.038$, power = 0.421; and external details, $F(1, 68) = 0.20$, $p = .657$, $\eta_p^2 = 0.003$, power = 0.071. The interaction between detail type and group status is shown in Figure 2, and tests of simple effects revealed that there were less external than internal details generated for both cannabis, $F(1, 68) = 93.82$, $p < .001$, $\eta_p^2 = 0.580$, power = 1.000 and substance naïve control group $F(1, 68) = 81.18$, $p < .001$, $\eta_p^2 = 0.544$, power = 1.000. However, while differences were significant for both groups, the difference is larger for the cannabis users compared to the control group. This difference seems to drive the interaction.

There is no indication of any differences between the groups in the number of details generated.

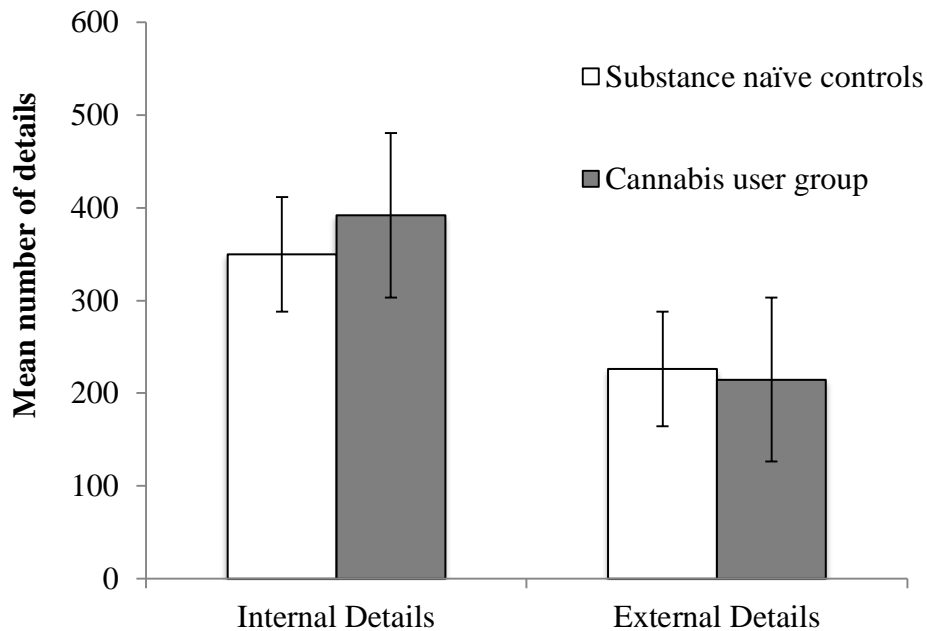


Figure 2. *Mean number of internal and external details generated on the AI as a function of group status (substance naïve control group, $n = 45$; cannabis user group, $n = 25$) (Error bars depict standard error of the mean)*

The second significant interaction between temporal direction and detail type is shown in Figure 3, and tests of simple effects revealed that there were significantly more internal details generated in the past condition than the future condition, $F(1, 68) = 128.82, p < .001, \eta_p^2 = 0.65$, but the number of external details generated in past and future condition did not differ significantly, $F(1, 68) = 128.82, p = 0.134, \eta_p^2 = 0.032$. Further analyses revealed that there were more internal than external details generated for both past condition $F(1, 68) = 218.44, p < .001, \eta_p^2 = 0.760$, and future condition, $F(1, 68) = 30.76, p < .001, \eta_p^2 = 0.308$.

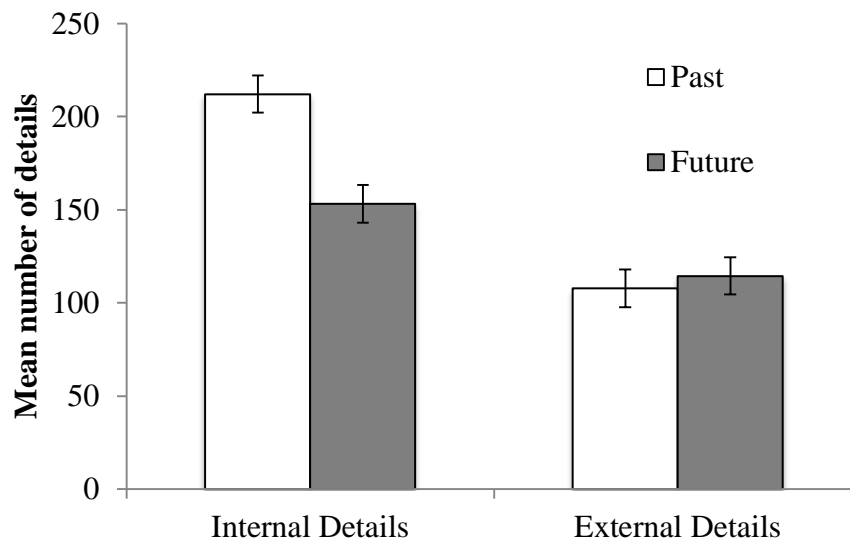


Figure 3. *Mean number of internal and external details generated on the AI as a function of temporal direction (past, future) (Error bars depict standard error of the mean)*

In summary, the key finding was that the groups did not differ in the number of internal or external details generated. Group status was not a main effect and did not interact with other variables except for the two way interaction of group status and detail type. However further analysis of this interaction showed there was not a significant difference between the groups in the number of internal or external details generated. There was one other significant interaction, between temporal direction and detail type. Analyses revealed that all participants generated more internal details for past than future conditions, while the number of external details did not differ between past and future conditions. Finally, all participants generated more internal than external details for both past and future conditions.

Correlations

Finally, in order to investigate cognitive correlates of episodic foresight, correlation analyses were conducted between episodic foresight (future internal details), and episodic

memory (past internal details) and the three measures of executive functioning for the two groups separately. Episodic foresight and episodic memory were strongly correlated for the control group ($r = .81$) and moderately correlated for the cannabis group ($r = .47$). The only executive function measure to correlate with episodic foresight in both groups was verbal fluency. However the correlation was large in magnitude for the cannabis group ($r = .56$), but only moderate sized for the control group ($r = .31$). No other correlations attained significance in either group.

Discussion

These data provide the first direct assessment of how the critical capacity for episodic foresight is affected by regular cannabis use. Contrary to predictions, the results showed that cannabis users generated a comparable number of episodic details when imagining novel future scenarios relative to substance naive controls. These results therefore indicate that cannabis use may not adversely affect capacity for episodic foresight. However, the results also provide no evidence of any impairment in episodic memory (as indexed by the number of past internal details on the AI), or executive functioning, which is not consistent with some previous studies which have identified deficits in these abilities (Curran et al., 2002; Ilan et al., 2004). These data indicate that cannabis, at least when used at the level engaged in by the current sample, may not have any influence on a broad range of cognitive functions, including episodic foresight. These results can therefore be regarded as positive news in light of the relatively large number of community dwelling adults (180 million users globally) that report using cannabis (United Nations Office of Drugs and Crime, 2014).

However, there are a number of important caveats and additional considerations that are likely to be important in interpreting these data. First, although the sample consisted of regular cannabis users, the average age that regular use was reported to commence was relatively high (19.34 years). Greater neurocognitive difficulties have been consistently

associated with early age of onset of cannabis use, usually in adolescence (see Lisdahl, Wright, Medina-Kirchner, Maple, & Scollenbarger, 2014 for review). It is therefore possible that there has been less disruption to neurodevelopment in the current cannabis sample than might be found in a sample whose cannabis use commenced earlier in adolescence (Gonzalez & Swanson, 2012).

Second, although this study did not collect data relating to the type of cannabis used by participants, in Australia the prevalence of high THC cannabis strains, such as synthetic products commonly sold as “skunk” or “kronic”, is very low (1.2% lifetime prevalence) compared to more natural varieties (38% lifetime prevalence) (Australian Institute of Health and Welfare, 2014). While high THC cannabis strains have been linked to greater neurocognitive impairment, there is now a growing literature showing that cannabis containing high levels of cannabidiol (CBD), can mitigate the amnesic, psychosis-like and attentional bias effects of THC (Morgan et al, 2010a, b). Consequently, the lack of episodic foresight difficulties (and other cognitive difficulties) observed in this cannabis using sample could be due to the type of cannabis consumed being high in CBD.

However, a third possible explanation for the absence of any group differences may relate to the use of compensatory mechanisms. It is not uncommon to observe an absence of compromised cognitive performance in the presence of alterations in neurological functioning within the context of cannabis use (Chang, Yakupov, Cloak, & Ernst, 2006; Elderth, Matochik, Cadet, & Bolla, 2004; Nestor, Hester, & Garavan, 2010; Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2010). It has been proposed that intact performance on some cognitive paradigms in this cohort may be due to the recruitment of extra brain regions to compensate for atrophy within required areas (Chang et al., 2006; Elderth et al., 2004; Nestor et al., 2010; Schweinsburg et al., 2010). The pattern of correlations identified in this study would appear to be at least broadly consistent with such a possibility. Specifically,

the weaker correlation between episodic foresight and episodic memory found for the cannabis user group compared to the control group may indicate that the cannabis group were less able to utilize episodic memory when constructing future scenarios. This have led them in turn to recruit more assistance from other cognitive processes to compensate for this leading to no difference in measured performance between the two groups. Such a possibility however awaits further empirical investigation.

Lastly, despite the lack of interaction between substance-use status and the type of event details generated from the interview, there appears to be a (albeit weak) trend in that there is a group difference in internal details but no difference in the generation of external details. Given the relatively light substance use reported by the cannabis-using participants, it is possible that the measures employed to assess episodic foresight are not sensitive enough to identify subtle deficits. Future investigations could aim towards assessing episodic foresight in samples of heavier or more frequent users. Alternatively (or additionally), a qualitative investigation of the type of details being generated by this substance-using group may assist in detecting subtle differences in episodic foresight ability within the context of cannabis-use.

Taken together, the present study indicates that cannabis use may not always disrupt cognitive function, and shows for the first time that this extends to the capacity for episodic foresight. In light of the current study involving a possibly unique group of cannabis users that were low level, late onset and used for relatively short period, future research is now needed to cross-validate these findings in a larger clinical cohort. In particular, it seems important to clarify how the capacity for episodic foresight might be affected across different levels of cannabis use, and the degree to which performance varies as a function of initial age of cannabis use. These are important questions in light of the widespread use of cannabis, and well-documented psychosocial consequences associated with its use. Specifically, a better understanding of when and why cognitive functioning is likely to be impacted in this

group could assist in the development of more tailored support and harm-minimization strategies.

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CHAPTER 10: Discussion

10.1 Introduction and chapter overview

The three studies presented in this research project were designed to examine episodic foresight ability in two different substance-using groups. The overall objectives across the three studies were:

Study 1:

- To investigate episodic foresight ability in a group of long term opiate users
- To determine whether memory and executive functions contribute to episodic foresight ability in the context of chronic, illicit substance use

Study 2:

- To explore whether the identified episodic foresight deficit obtained in Study 1 may be attributable to compromised scene construction, self-projection, and/or narrative ability

Study 3:

- To investigate whether episodic foresight ability would also be impaired in a group of regular cannabis users
- To determine whether memory and executive function contribute to episodic foresight ability in the context of regular cannabis use

The findings from all three studies represent the first assessment of episodic foresight within the context of psychoactive substance use. The data demonstrate differences in episodic foresight ability across different substance-using groups, highlighting the variable impact of psychoactive drugs on human cognition. This chapter begins with summaries and a combined discussion of the first two studies focusing on opiate users, followed by a summary

and discussion of the third study. The discussions focus on the theoretical and clinical implications of these results. Limitations and strengths of the overall project are presented before a concluding paragraph summarising the overall project.

10.2 Study 1 summary of results

This study was conducted to address a noticeable gap in the literature regarding an absence of investigations examining episodic foresight ability in *any* substance-using group. Consistent with the first hypothesis formulated for this initial study, the opiate user group demonstrated compromised episodic foresight ability in comparison to a healthy control group. When instructed to imagine and subsequently describe themselves in a novel future scenario, the opiate group experienced significant difficulty generating details that were specific to their own personal experience. Their inability was further reinforced by generation of a larger number of off-topic details such as semantic information or repetitions of events they had already previously-experienced. The findings of Study 1 only partially supported the second hypothesis that predicted relationships between episodic foresight and episodic memory, and executive control. Despite no difference in episodic memory ability between the two groups, a significant relationship between episodic memory and episodic foresight was found for both opiate users and controls, supporting the notion that these two faculties rely on similar neural substrates. Contrary to predictions, executive control did not differ between the two groups, nor did it correlate with episodic foresight in either group.

10.3 Study 2 summary of results

Study 2 was conducted to better understand the mechanisms underlying the deficit in episodic foresight amongst opiate users identified in Study 1. More specifically, this follow up investigation aimed to address whether this deficit reflected compromised scene construction, self-projection, or narrative ability. As anticipated the opiate user group

performed less well than the control group when asked to imagine and describe a personally relevant future scenario, confirming a deficit in episodic foresight. However this study provided further insight into the potential mechanisms underlying this deficit. Relative to the control group the opiate user group generated fewer personally relevant details when instructed to provide a narrative based on a predefined story structure as well as when instructed to imagine experiencing an event in their personal future. This initial result suggested that opiate-related episodic foresight deficits are a function of both narrative ability and self-projection. However on further inspection of within group performance, both the control and opiate groups performed better in the narrative task relative to the self-projection task. Given that the scenario cue used in the narrative condition provided participants with a detailed story structure, there was a lesser demand for independent scene construction. The opiate user group however performed much worse on the task requiring self-projection relative to their narrative performance. Consequently, episodic foresight deficits in chronic opiate users may be explained by an inability to projection the self into a novel future which is not secondary to narrative ability.

10.4 Contributions and implications of studies 1 and 2

The findings from Study 1 provide the first direct evidence that episodic foresight is impaired within the context of chronic opiate use, and indicate that this deficit is not secondary to impairments in memory or executive control. Furthermore, studies 1 and 2 provide support for the constructive simulation hypothesis that postulates that memories (episodic) are the basic materials used for future event construction. Study 2 in particular shows that other cognitive processes such as self-projection are recruited in order to construct and pre-experience novel future events. The findings of these first two studies highlight the complex nature of episodic foresight, which is considered to be more cognitively demanding than episodic memory. Also, this behavioural evidence from the first two studies is consistent

with the suggestion that compromised foresight ability may be a reflection of abnormalities in areas of the brain known to be functionally and structurally altered within the context of chronic opiate use and that are established as being associated with episodic foresight (such as the MTL).

While theoretically important, the data from the first and second studies of this project also have significant implications for the treatment of long-standing substance dependence. Poor treatment compliance and high relapse rates are particularly common among long-term opiate users attempting to achieve abstinence from their addiction (Smyth, Barry, Keenan, & Ducray, 2010). Therefore the identification of an episodic foresight deficit within the context of chronic opiate use can be useful in informing the modification of treatment protocols used alongside front line pharmacotherapies. For example, Motivational Interviewing (MI) strategies often used in the treatment of addiction, aim to address ambivalence towards change by promoting intrinsic motivation towards behaviour modification (Arkowitz & Miller, 2008). A commonly used tool in MI is decisional balancing which focuses on an individual's ambivalence towards behaviour change (Miller & Rollnick, 2009). This process requires generating positive and negative consequences that would occur as a result of changing behaviour in order to encourage intrinsic motivation to initiate the change process (Miller & Rollnick, 2009). In the context of substance dependence this could involve considering possible outcomes associated with the cessation of compulsive drug use. The concept of a drug free existence would be a very foreign concept for many opiate users, particularly chronic opiate users given that opiate use tends to be initiated after an extensive period of other substance use (Fernández-Serrano et al., 2011). Given the breakdown in episodic foresight, the generation of positive outcomes associated with drug-free living may be particularly difficult for a long term user to personally imagine and pre-experience, therefore hindering the promotion of intrinsic motivation towards changing problem drug-

using behaviour. This suggests some alterations may need to be made to this aspect of treatment to accommodate episodic foresight deficits in order to maximise successful outcomes.

However, even for those who seek treatment already motivated to change their problem behaviour (Arkowitz & Miller, 2008) episodic foresight deficits may also hinder treatment success. This is because in these cases, interventions become more goal-directed. Such interventions include developing a plan for change. This involves deciding on what exactly needs to change in a client's life and generating more adaptive behavioural contingencies that promote the achievement of these changes. In order to encourage motivation towards a modified lifestyle, the client would be encouraged to envision a future that includes the changes they would like to achieve (Arkowitz & Miller, 2008). With a reduced capacity for episodic foresight, treatment success again is likely to be reduced.

In studies 1 and 2 participants showered compromised episodic foresight when instructed to imagine future event three years and one year into the future, respectively. These findings suggest that relapse prevention protocols that require clients to picture their future if they made desired changes should not focus on assisting clients to set goals well ahead in the future, but rather should emphasise short term treatment objectives. Better treatment compliance and prognosis may result if treatment is focused more on fulfilling immediate treatment related goals, which are in line with the client's current needs, such as simply remembering therapy appointments. Constructing long-term abstinence goals may be too difficult for this clinical group and may be hard for them to imagine themselves realistically achieving. Overall, the findings of the first two studies of this research project do not suggest a complete revolution of current treatment methods, but rather indicate that modification may be beneficial such that there is less demand for future-oriented thinking during the treatment of long-term opiate use.

10.5 Study 3 summary of results

Given the existing evidence for cannabis-related impairments in a range of cognitions such as learning, memory, and executive processing (Abdullaev et al., 2010; Bolla et al., 2005; Curran et al., 2002; Solowij et al., 2002), the primary goal of Study 3 was to explore whether episodic foresight deficits would also be observed in the context of regular cannabis use. Similar to Study 1 the secondary objective was to explore the relationships between episodic foresight and episodic memory, and executive control. To address these questions this study administered the same neurocognitive battery employed in Study 1. In contrast to Study 1, the findings of this third study did not find cannabis-related impairments in episodic foresight, with the cannabis group's ability to generate personally relevant details of novel future events comparable to the substance naïve control group. There was also no cannabis-related memory impairment observed in this third study. However the findings did support the notion that episodic memory contributes to the capacity to construct and pre-experience novel future experiences, as similar to Study 1, a relationship was observed between episodic foresight and episodic memory in both experimental groups. A relationship between episodic foresight and executive functioning (as indexed by performance on a measure of verbal fluency) was also identified in both groups suggesting a role for executive control in episodic foresight, which had not been apparent for either group in Study 1.

10.6 Contributions and implications of study 3

These data add to the currently inconsistent literature relating to cannabis-related cognitive functioning. As previously noted there is ongoing debate over the neurotoxicity of cannabis in humans and the literature provides strong evidence both for (Abdullaev et al., 2010; Bolla et al., 2005; Curran et al., 2002; Morgan, Schafer, et al., 2010; Solowij et al., 2002) and against (Chang et al., 2006; Elderth et al., 2004; Nestor et al., 2010; Schweinsburg et al., 2010) potentially damaging neurocognitive outcomes. The findings of Study 3 suggest

that cognitive functioning, at least in terms of episodic foresight ability, is spared in the context of cannabis use. However there are a number of explanations that may account for the absence of group differences in episodic foresight that should be considered before this conclusion can be confidently made.

First, the cannabis-using group recruited for Study 3 reported a relatively later age of cannabis initiation (over 18 years old). This sample characteristic is particularly notable because earlier introduction to cannabis use, particularly during early adolescence, is associated with greater cannabis-related cognitive impairments (Gonzalez & Swanson, 2012; Hall, 2014; Lisdahl, Wright, Medina-Kirchner, Maple, & Scollenbarger, 2014). Given the later age of onset reported in this cannabis-using sample it is possible that neurological development followed the typical trajectory prior to initiation of use, therefore allowing for intact cognitive processing.

Second, the strain of cannabis used can have a significant impact on cognitive outcomes with recent studies demonstrating greater cognitive impairment as a function of its pharmacological makeup (Morgan, Freeman, Schafer, & Curran, 2010; Morgan, Schafer, et al., 2010). This pharmacological make up can vary significantly depending on the region the cannabis is grown in and methods of growth. It should therefore be considered that the lack of group differences in Study 3 might to some extent be a function of the strain of cannabis used by the participants.

However, another arguably stronger argument for the lack of episodic foresight impairment observed within the context of cannabis use may relate to the use of compensatory mechanisms. Despite neuroimaging studies observing cannabis-related alterations in neurological functioning, the performance of cannabis-using individuals across various cognitive paradigms have been shown to be comparable to healthy control participants (Chang et al., 2006; Elderth et al., 2004; Nestor et al., 2010; Schweinsburg et al.,

2010). For example, Chang et al. (2006) observed lower activation in prefrontal, medial, and parietal brain regions, but increase activity within the cerebellum of active cannabis users, relative to healthy controls. However behavioural performance on a battery of neuropsychological assessments for functions including memory, attention, and executive functioning, was comparable between the cannabis and control groups. Similarly, a study by Schweinsburg et al. (2010) showed that when completing a task of spatial working memory, adolescent cannabis users had greater brain activity in prefrontal regions and the anterior insula than controls, but performance on the spatial working memory task did not differ between the two groups. Studies such as these proposed that the lack of differences in cognitive abilities in the presence of abnormal neural functioning may be the result of non-related brain regions being recruited to compensate for atrophy in the associated areas required for intact processing (Chang et al., 2006; Elderth et al., 2004; Nestor et al., 2010; Schweinsburg et al., 2010). This is therefore one other possible explanation of the lack of episodic foresight deficit in cannabis users in the current research project.

Despite no cannabis-related deficit in episodic foresight identified in Study 3, these data provide a platform for further investigation of the circumstances in which cannabis use might influence episodic foresight ability. As discussed in Chapters 2 and 9 (Study 3), cannabis continues to be the world's most used illicit drug and despite the general perception that it is a benign substance (United Nations Office of Drugs and Crime, 2014) early introduction to the drug can significantly alter neuronal development and increase the likelihood of developing future addiction by six fold. Furthermore, regular cannabis use is associated with a number of deleterious psychosocial consequences (Hall, 2014; Parker et al., 2002; Wagner & Anthony, 2002). Therefore it is particularly important to investigate drug specific cognitive declines across all stages of consumption, even at the very early stages as

greater knowledge could assist in the development of more tailored support and harm-minimization strategies that could prevent evolution into addictive behaviours.

10.7 Limitations of the overall research project

One limitation of this research project relates to the heterogeneity of substance use history among participants, particularly in the first two investigations. As mentioned throughout this project, it is unlikely that opiates are the drug of preference for novice users, therefore it is almost inevitable that opiate-dependent individuals have an extensive history of poly drug abuse and/or dependence. In addition, poly drug use was also reported in some of the cannabis-using participants recruited in Study 3. Furthermore the opiate sample recruited for Study 1 was participating in opiate substitution treatment which is the first line treatment option for opiate dependence (United Nations Office of Drugs and Crime, 2014). The most common type is Methadone, but other substitutes include Buprenorphine, Naloxone, and Suboxone (which is a combination of the latter two). These substitutes induce less euphoria and are longer acting substances than opiates which aim to relieve physiological cravings for opiates (United Nations Office of Drugs and Crime, 2014). However some studies have identified cognitive declines associated with these substitutes (Curran et al., 2001; Darke et al., 2000) and thus it is difficult to delineate the effects of opiates from other substances, including the effects of pharmacotherapies.

Second, a larger battery of neuropsychological measures could have been administered to assess a wider range of cognitive and executive functions. For example, including an additional measure of episodic memory would have allowed for more thorough assessment of this ability. However in saying that, the length of time required to administer the chosen battery was already substantial and increasing this could have been at a cost to the reliability of interpretation and participant engagement. This is because participants in the opiate group were already required to have refrained from consuming methadone for slightly

a longer period than they normally would have, and to have increased the testing time further would have increased the risk of withdrawal and cravings, potentially impacting engagement and performance on tasks.

Third, information relating to psychiatric comorbidities, and confirmation of abstinence from any psychoactive substances (including alcohol) 24 hours prior to testing were obtained via self-report. It would have been preferable to have drug screening analysis and access to psychiatric diagnosis details from independent sources, but the sample was recruited from the general public and therefore these details were not available.

Finally, conclusions relating to the involvement and overlap of neural substrates across all three studies are speculative at best given the lack of neuroimaging evidence. However, these suggestions are based on pre-existing neuroimaging studies that have implicated the involvement of similar neural mechanisms in the execution of episodic foresight, as well as areas which have been shown to attract structural and functional atrophy within the context of substance use.

10.8 Strengths of the overall research project

Despite some limitations, this research project had a number of strengths. For instance, although there was reliance on self-report, all individuals underwent a number of intake interviews prior to their testing sessions and individuals who reported inconsistencies on responses relating to drug use history, mental health diagnosis, and history of brain injury between interviews (as well as those who disclosed ineligibility during testing) were not included in the project.

A second strength relates to the representativeness of the opiate samples. Instead of recruiting individuals from residential treatment facilities, the opiate users who were involved in Studies 1 and 2 were recruited from the general public through services that dispensed their

pharmacotherapy as well as organisations that provided support specifically for injecting drug users. Despite the well-known physical, psychological, social, and functional difficulties associated with opiate use, the samples recruited for studies 1 and 2 are representative of a high-functioning subset of a clinical group as their participation in this research project was reliant on their personal motivation to attend as well as their capacity to do so. Therefore, the findings of Studies 1 and 2 could certainly translate to real life application as the opiate users recruited for this project represent individuals who would most likely present to community provided treatment services.

Lastly, the sample sizes of the three investigations were large compared to clinical samples recruited for previous studies investigating episodic foresight, as well as those assessing the cognitive impact of opiate and cannabis use (see Table 2 below). Furthermore it should be noted that despite the challenges associated with recruiting from the community all three studies conducted for this research project are comparable to, and indeed exceed most of the sample sizes those of substance-related investigations which predominately recruit through treatment facilities.

10.9 Conclusion

This research project is the first to directly examine the capacity for episodic foresight in the context of psychoactive substance use. Prior to this research project, the capacity for episodic foresight within substance-using groups could only be inferred from investigations of cognitive abilities that incorporated an element of future-oriented thought. The findings of the three studies make a significant contribution to the literature relating to the cognitive functioning of substances users, and are an addition to the evolving literature relating to episodic foresight ability. The unique findings of these three studies provide a platform for future investigations into the cognitive capacities of substance users which may have

profound implications for the way services approach the treatment of problematic substance use.

Table 2.

Sample sizes of previous studies investigating episodic foresight, opiate use, and cannabis use

Episodic foresight studies			Opiate studies			Cannabis studies		
Authors	Groups	<i>n</i>	Authors	Groups	<i>n</i>	Authors	Groups	<i>n</i>
Addis et al. (2008)	Healthy older adults	16	Pezawas et al. (1998)	Opiate group	21	Lundqvist et al. (2001)	Cannabis group	14
	Healthy younger adults	16		Healthy controls	21		Healthy controls	14
D'Argembeau,	Schizophrenia	16	Ornstein et al. (2000)	Opiate group	22	Curran et al. (2001)	Cannabis group	15
Raffard, et al. (2008)	Healthy controls	16		Amphetamine group	23			
D'Argembeau et al. (2010)	Healthy adult males	16	Lyyo et al. (2004)	Healthy controls	22	Block et al. (2002)		
				Opiate group	32		Cannabis group	18
				Cocaine group	32		Healthy controls	13
Lind and Bowler (2010)	ASD (adults)	14	Mintzer, Copersino, and Stitzer (2005)	Healthy controls	32	Solowij et al. (2002)	Cannabis (long-term)	51
	Healthy controls	14		Opiate group	20		Cannabis (short-term)	51
Raffard et al. (2010)	Schizophrenia	24		Amphetamine group	18		Healthy controls	33
	Healthy controls	25	Lyyo et al. (2006)	Healthy controls	21	Elderth et al. (2004)	Cannabis group	11
Squire et al. (2010)	Amnesic patients	5		Healthy controls	46		Healthy controls	11
	Healthy controls	5	Fu et al. (2008)	Opiate group	30	Ilan, Smith, and Gevins (2004)	Cannabis group	10
de Vito et al. (2012)	PD patients	31		Healthy controls	18	Matochik et al. (2005)	Cannabis group	11
	Healthy controls	31	Wang et al. (2012)	Opiate group	21		Healthy controls	8
Rendell et al. (2012)	Healthy older adults	25		Healthy controls	20	Chang et al. (2006)	Cannabis group	24
	Healthy younger adults	24	Cheng et al. (2013)	Opiate group	33		Healthy controls	19
Lind et al. (2014)	ASD (adults)	27		Healthy controls	30	Morgan, Schafer, et al. (2010)	Cannabis group	134
	Healthy controls	26	Terrett et al. (2014)	Opiate group	26			
				Healthy controls	35			

Note: ASD = Autism Spectrum Disorder, PD = Parkinson's Disease

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Appendices.

Appendix A Human Research Ethics Committee Original Study Approval



Human Research Ethics Committee Committee Approval Form

Principal Investigator/Supervisor: Gill Terrett Melbourne Campus

Co-Investigators: Peter Rendell Melbourne Campus

Student Researcher: Kimberley Mercuri Melbourne Campus

Ethics approval has been granted for the following project:

An investigation into cognitive processing abilities of recreational drug users

for the period: 2/3/2011 - 2/7/2011

Human Research Ethics Committee (HREC) Register Number: V2010 135

Special Condition/s of Approval

Prior to commencement of your research, the following permissions are required to be submitted to the ACU HREC:
N/A

The following standard conditions as stipulated in the *National Statement on Ethical Conduct in Research Involving Humans* (2007) apply:

- (i) that Principal Investigators / Supervisors provide, on the form supplied by the Human Research Ethics Committee, annual reports on matters such as:
 - security of records
 - compliance with approved consent procedures and documentation
 - compliance with special conditions, and
- (ii) that researchers report to the HREC immediately any matter that might affect the ethical acceptability of the protocol, such as:
 - proposed changes to the protocol
 - unforeseen circumstances or events
 - adverse effects on participants

The HREC will conduct an audit each year of all projects deemed to be of more than low risk. There will also be random audits of a sample of projects considered to be of negligible risk and low risk on all campuses each year.

Within one month of the conclusion of the project, researchers are required to complete a *Final Report Form* and submit it to the local Research Services Officer.

If the project continues for more than one year, researchers are required to complete an *Annual Progress Report Form* and submit it to the local Research Services Officer within one month of the anniversary date of the ethics approval.

Signed:  Date:02/03/2011.....
(Research Services Officer, Melbourne Campus)

Appendix B Participant Recruitment and Informed Consent

Appendix B – 1 Expression of Interest (opiate group)



PARTICIPANTS NEEDED

Participants are needed for a research project looking into thinking and emotion processes of people who have had a history of heroin dependence.

- Testing is conducted at Australian Catholic **Fitzroy**
- It takes approximately **1.5 – 2hrs** to complete
- **Financial reimbursement** provided

Participants need to fulfill **ALL** of the following criteria to be eligible

- Over **18**
- Currently **stable on methadone, suboxone or similar treatment**
- **No** history of **head injury** that has led to hospitalisation
- **No** diagnosis of **acquired or traumatic brain injury** (ABI or TBI)
- **No** formal **psychiatric diagnoses** (for example: schizophrenia, bipolar, PTSD)
- **No** history of **alcohol dependence**

If you fulfil **ALL** the criteria, want more info or are interested in participating please **text YOUR NAME & RESEARCH INTEREST to 0434 244 199** (checked daily)
Or call 9953 3243 and leave your name and number.
One of our student researchers will call you back!!

This project is being conducted by Kimberly Mercuri, Dr Gill Terrett and Professor Peter Rendell of the Australian Catholic University. It has been approved by the ACU Human Research Ethics Committee. Ref No V2010 135

Appendix B – 2 Information Letter**INFORMATION LETTER**
*Copy for Participant to Keep***TITLE OF PROJECT:** Future thinking and drug use**PRIMARY STAFF SUPERVISOR:** Dr. Gill Terrett**CO - STAFF SUPERVISOR:** Prof Peter Rendell**STUDENT RESEARCHER:** Ms. Kimberly Mercuri**COURSE:** Masters of Psychology (Clinical)/PhD**SCHOOL OF
PSYCHOLOGY**

Australian Catholic University Limited
ABN 15 050 192 660
Melbourne Campus (St Patrick's)
115 Victoria Parade, Fitzroy, Vic. 3065
Locked Bag 4115 Fitzroy MCD VIC 3065
Telephone 03 9953 3000 Facsimile 03 9953
3005
www.acu.edu.au

Dear Participant,

You are invited to take part in a research project on illicit drug use and the ability to mentally time travel into the future and pre-experience an event. This type of thinking has been linked to other important functions such as memory, which are needed for successful completion of basic everyday tasks. This project involves one group of participants who currently engage in an opiate substitution program, and a comparison group of participants who do not have a history of substance abuse or dependence. Participants will be asked to complete an individual testing session of up to three hours at a mutually convenient time. Testing will take place at the Australian Catholic University, Melbourne Campus or at a mutually convenient location. During this time participants will complete a background questionnaire, question and answer tasks, as well as a brief interview. In appreciation for your participation, you will be financially reimbursed for your time at a rate of \$10 per hour. Qualifying undergraduate psychology students will also receive course credit.

Participants will not be asked to take any illicit substances. Indeed, *consent cannot be given or activities completed if the participant arrives at the testing situation under the influence of any substance or has consumed any drugs in the past 24 hours.* This study will not involve any diagnosis or treatment of drug use problems. Participants with concerns about their health and/or regarding drug use should contact their general practitioner or drug use hot line such as Turning Point: alcohol and drug centre direct line – 1800 888 236. ACU students can contact the university's counselling services; and for those who require a psychological referral, Dr. Barbara Jones of ACU Melbourne can also be contacted.

The primary investigator of this study is Miss Kimberly Mercuri who is currently completing her Masters of Psychology/Doctor of Philosophy at the Australian Catholic University, Melbourne campus. The testing session will involve the following.

- **Background Questionnaire:** This questionnaire asks you to indicate your age, gender, level of education, level of English and a general rating of your health. If you are a regular user of recreation drugs you will also be asked to indicate the type/s of drugs regularly consumed, quantity, frequency and duration of drug use. If you have never used illicit drugs, you will be asked to confirm that you have no significant history of any other substance use, or previous psychiatric or brain injury diagnoses. If you are unable to confirm this, unfortunately you do not

meet the criteria for being included in this study. You will not be asked to answer any other questions related to drug use.

- **Background Tests:** There are several background tests. They will require you to pronounce words, complete sentences, complete a puzzle, and verbally describe pictures. Any verbal responses will be transcribed by the student researcher, and one task will require audio recording of answers.
- **Interview:** Participants will be provided with various cue words and asked to remember or imagine personally relevant experiences related to the cues provided. The interview will be audio taped and later independently transcribed in order to analyse and score the verbal responses provided by participants. Identifying information will not be requested during the interview.

Participation in this research project is voluntary. You are free to withdraw from the study at any stage without giving reason. As identifying information will be not kept with the data at any stage, it will not be possible to withdraw your data once you have completed the testing session and submitted the data.

The researchers will take every reasonable precaution to maintain your confidentiality. Names or any identifying information will not be recorded on any of the raw data or kept with any of the processed data; and consent forms will be submitted separately and kept separate to raw data. The only information kept with the data will be the information outlined in the description of the biographical questionnaire (sex, age in years, and years of education, general health rating, drug use rating). Hand written responses are minimise with an electronic version of the background questionnaire which requires participants to check the relevant boxes. Individual participants or their results will not be identified in any future presentation of the results; only group results will be presented in any report. Also, given that illicit substance use is unlawful, the researchers cannot guarantee that a third party could not use some legal process to gain access to the data. It is stressed that identifying information will not be kept with the data in order to make re-identifying data difficult.

Any questions regarding this project can be directed to the staff supervisors: Dr. Gill Terrett and Assoc. Prof Peter Rendell in the School of Psychology, St. Patrick's Campus (Australian Catholic University, 115 Victoria parade, Fitzroy 3065).

Dr. Gill Terrett
Phone: 03 9953 3121
Fax: 03 9953 3205
Email: Gill.Terrett@acu.edu.au

Professor Peter Rendell
Phone: 03 9953 3126
Fax: 03 9953 3195
Email: Peter.Rendell@acu.edu.au

The Human Research Ethics Committee at Australian Catholic University has approved this study. In the event that you have any complaint or concern about the way you have been treated during the study, or if you have any query that the Student Researcher and Staff Supervisor have not been able to satisfy, you may write to:

Chair, Human Research Ethics Committee
C/o Research Services
Australian Catholic University
Locked Bag 4115
FITZROY, VIC. 3065

Ph: 03 9953 3157 Fax: 03 9953 3315

Any complaint will be treated in confidence and investigated fully. The participant will be informed of the outcome.

If you are willing to participate please sign the attached informed consent forms. You should sign both copies of the consent form and keep one copy for your records and return the other copy to the staff supervisor.

Your support for the research project will be most appreciated.

Miss. Kimberly Mercuri
Research Student

Dr. Gill Terrett
Primary Staff Supervisor

Professor Peter Rendell
Co - Staff Supervisor

Date:

Date:

Date:

Appendix B – 3 Consent Forms**Appendix B – 3.1 Copy for Participants****INFORMED CONSENT*****Copy for Participants to Keep*****TITLE OF PROJECT:** Future thinking and drug use**PRIMARY STAFF SUPERVISOR:** Dr. Gill Terrett**CO - STAFF SUPERVISOR:** Professor Peter Rendell**STUDENT RESEARCHER:** Ms. Kimberly Mercuri**COURSE:** Masters of Psychology (Clinical)/PhD**SCHOOL OF PSYCHOLOGY**

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Participants section

I (*the participant*) have read and understood the information in the letter inviting participation in this research project, and any questions I have asked have been answered to my satisfaction. I agree to participate in this study realising that I can withdraw at any time.

Please Tick:

- ☐ I agree to participate in the activities as outlined in the Information Letter. This involves completing a testing session taking up to three hours comprising of answering a background questionnaire, several background tests, computerized tests, and a brief interview.
- ☐ I agree to the audio taping of my responses to the sentence completion task and the one-on-one interview as outlined in the Information Letter.
- ☐ I agree to participate in this activity realising that information gathered will remain confidential and secure except when:
 - ♦ It is required by Law
 - ♦ Failure to disclose the information would place you or another person at risk,

OR

- ♦ Researchers have obtained your prior approval to share your information with a third party
- ☐ I agree that research data collected for the study may be published or provided to other researchers in a form that does not identify me in any way.
- ☐ I am over 18 years of age.

Name: Signature: Date:

Miss. Kimberly Mercuri
Research Student

Date:

Dr. Gill Terrett
Primary Staff Supervisor

Date:

Professor Peter Rendell
Co - Staff Supervisor

Date:

*Appendix B – 3.2 Copy for Researcher***INFORMED CONSENT*****Copy for Researcher*****TITLE OF PROJECT:** Future thinking and drug use**PRIMARY STAFF SUPERVISOR:** Dr. Gill Terrett**CO - STAFF SUPERVISOR:** Professor Peter Rendell**STUDENT RESEARCHER:** Ms. Kimberly Mercuri**COURSE:** Masters of Psychology (Clinical)/PhD**SCHOOL OF PSYCHOLOGY**
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 Telephone 03 9953 3000 Facsimile 03 9953 3005
 www.acu.edu.au
Participants section

I (*the participant*) have read and understood the information in the letter inviting participation in this research project, and any questions I have asked have been answered to my satisfaction. I agree to participate in this study realising that I can withdraw at any time.

Please Tick:

- ☐ I agree to participate in the activities as outlined in the Information Letter. This involves completing a testing session taking up to three hours comprising of answering a background questionnaire, several background tests, computerized tests, and a brief interview.
- ☐ I agree to the audio taping of my responses to the sentence completion task and the one-on-one interview as outlined in the Information Letter.
- ☐ I agree to participate in this activity realising that information gathered will remain confidential and secure except when:
 - ♦ It is required by Law
 - ♦ Failure to disclose the information would place you or another person at risk,

OR

- ♦ Researchers have obtained your prior approval to share your information with a third party
- ☐ I agree that research data collected for the study may be published or provided to other researchers in a form that does not identify me in any way.
- ☐ I am over 18 years of age.

Name: Signature: Date:

 Miss. Kimberly Mercuri
 Research Student
 Date:

 Dr. Gill Terrett
 Primary Staff Supervisor
 Date:

 Professor Peter Rendell
 Co - Staff Supervisor
 Date:

Appendix C Background Measures**Appendix C – 1 Demographic Questionnaire**

Background Questionnaire (methadone sample cover)

To participate in this study you need to confirm all of the following statements. If you are unable to confirm ALL of the statements, unfortunately you are not eligible to participate in this study.

1. I am over 18 years old
2. I have a history of heroin dependence
3. I am currently participating in a methadone maintenance program for my
heroin dependence
4. I do not have a history of head injury that led to hospitalization
5. I do not have any formal diagnosis of Traumatic Brain Injury (TBI) or Acquired
Brain injury (ABI)
6. I have been stable on my methadone for at least 2 weeks
7. I have not consumed my methadone in the last 5 hours
8. I have not used heroin or other illicit drugs within the last 24 hours
9. I have never been a heavy drinker of alcohol. This is regularly drinking to
intoxication or having more than 28 standard drinks per week if you are male, or
more than 14 standard drinks per week if you are female.
10. English is my first language

Background Questionnaire (control sample cover)

To participate in this study you need to confirm all of the following statements. If you are unable to confirm ALL of the statements, unfortunately you are not eligible to participate in this study.

1. I am over 18 years old
2. I do not have a history of alcohol or drug dependence
3. I do not have a history of head injury that led to hospitalization
4. I do not have any formal diagnosis of Traumatic Brain Injury (TBI) or Acquired Brain injury (ABI)
5. I have not used alcohol or any other illicit drug within the last 24 hours
6. I have never been a heavy drinker of alcohol. This is regularly drinking to intoxication or having more than 28 standard drinks per week if you are male, or more than 14 standard drinks per week if you are female.
7. English is my first language

Section 1: Demographics

Age: _____ years **Gender** *(please tick)*: Male ☐ Female ☐ Other *(please specify)* _____

Relationship Status:

- ☐ Married
☐ Living together/defacto
☐ Partnered but not living together
☐ Separated/divorced
☐ Single

Number of children:

- ☐ 0
☐ 1
☐ 2
☐ 3
☐ More than 3

Employment Status:

- ☐ Full-time
☐ Part-time
☐ Casual
☐ Unemployed

Highest level of education completed:

- ☐ Up to Year 10
☐ Up to Year 12
☐ TAFE
☐ Undergraduate degree
☐ Postgraduate degree
☐ Other, please specify _____
-

Section 2: English Language Skills

Is English your first language: Yes _____ No _____

If NO, how many years have you spoken English? _____ years

How do you rate your level of English?

Excellent ☐ Very good ☐ Not very good ☐ Poor ☐

Section 3: Health

Using the following as a guide please answer the questions below. Please tick the box that best describes you.

Excellent: No problems

Very good: no major problems

Good: occasional bad days

Not very good: a number of problems

Poor: Persistent serious problems

How would you describe your state of health over the last month or so?

Excellent ☐ Very good ☐ Good ☐ Not very good ☐ Poor ☐

How would you describe your state of health today?

Excellent ☐ Very good ☐ Good ☐ Not very good ☐ Poor ☐

How would you describe how you have been sleeping over the last few weeks?

Excellent ☐ Very good ☐ Good ☐ Not very good ☐ Poor ☐

Section 4: Psychiatric History

Are you aware of any formal psychiatric diagnoses? Yes ☐ No ☐

If YES, please specify:

Section 5a: Substance use

The following section asks about current and past use of alcohol and drugs. For each drug please indicate whether you are a ***current user, have used in the past, or have never used*** the substance.

If you are a **current user** or **have used this substance in the past** please indicate:

- The age of first use
- The age of regular use (if applicable)
- How often you use
- How much of the drug you would use
- How long you used the drug

For any substance you have used please tick NEVER, and continue to the next drug.

If you have **never used any type of drugs** you do not have to complete this section.

AlcoholCurrent use ☐ Past use ☐ Never ☐

Age of first use: ____ years Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> 1-6 standard drinks each week	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> 7-14 standard drinks each week	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> 15-21 standard drinks each week	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> 22-27 standard drinks each week	<input type="checkbox"/> 3-5 years
<input type="checkbox"/> Never/once or twice	<input type="checkbox"/> 28 or more standard drinks each week	<input type="checkbox"/> More than 5 years

CigarettesCurrent use ☐ Past use ☐ Never ☐

Age of first use: ____ years Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> few cigarettes a day	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> less than a packet a day	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> a packet a day	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> more than a packet a day	<input type="checkbox"/> 3-5 years
<input type="checkbox"/> Never/once or twice	<input type="checkbox"/> Other	<input type="checkbox"/> More than 5 years

CannabisCurrent use ☐ Past use ☐ Never ☐

Age of first use: ____ years Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> 1-3 joints at a time	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> 4-6 joints at a time	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> 7 or more joints at a time	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> Other:	<input type="checkbox"/> 3-5 years
		<input type="checkbox"/> More than 5 years

Amphetamines (e.g speed, ecstasy, ice, MDMA) Please specifyCurrent use ☐ Past use ☐ Never ☐

Age of first use: ____ years Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> 1 pill at a time	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> 2-3 pills at a time	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> more than 3 pills at a time	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> Other:	<input type="checkbox"/> 3-5 years
		<input type="checkbox"/> More than 5 years

HeroinCurrent use ☐ Past use ☐ Never ☐

Age of first use: ____ years Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> 1 hit at a time	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> 2-3 hits at a time	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> more than 4 hits at a time	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> Other:	<input type="checkbox"/> 3-5 years
	1 hit = 0.3g heroin	<input type="checkbox"/> More than 5 years

CocaineCurrent use ☐ Past use ☐ Never ☐

Age of first use: ____ years Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> 1 line at a time	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> 2-3 lines at a time	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> more than 4 lines at a time	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> Other:	<input type="checkbox"/> 3-5 years
		<input type="checkbox"/> More than 5 years

LSD/AcidCurrent use ☐ Past use ☐ Never ☐

Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> 1-3 tabs at a time	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> 3-5 tabs at a time	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> 5 or more tabs at a time	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> Other:	<input type="checkbox"/> 3-5 years
		<input type="checkbox"/> More than 5 years

Prescription medications (e.g. Vallium, Xanax, Seroquel)Current use ☐ Past use ☐ Never ☐

Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week	<input type="checkbox"/> 1 pill at a time	<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight	<input type="checkbox"/> 2-3 pills at a time	<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month	<input type="checkbox"/> more than 3 pills at a time	<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month	<input type="checkbox"/> Other:	<input type="checkbox"/> 3-5 years
		<input type="checkbox"/> More than 5 years

Section 5b: Substance use

If there drug/s you have used have not already been specified, please provide details in the space provided below.

Other _____

Current use ☐ Past use ☐ Never ☐

Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week		<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight		<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month		<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month		<input type="checkbox"/> 3-5 years
		<input type="checkbox"/> More than 5 years

Other _____

Current use ☐ Past use ☐ Never ☐

Age of regular use: ____ years

Frequency	Dosage	Duration
<input type="checkbox"/> At least once a week		<input type="checkbox"/> less than 6 months
<input type="checkbox"/> At least once a fortnight		<input type="checkbox"/> 6 months – 1year
<input type="checkbox"/> At least once a month		<input type="checkbox"/> 1-3 years
<input type="checkbox"/> Less than once a month		<input type="checkbox"/> 3-5 years
		<input type="checkbox"/> More than 5 years

Section 6: Methadone

What is your current methadone dose: _____

How long have you been on this dose: _____

How long have you been stable on this dose: _____

Appendix C – 2 National Adult Reading Test

National Adult Reading Test (NART)

SECOND EDITION

Word Card

Hazel E. Nelson

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DÉBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DETENTE
EQUIVOCAL	IDYLL
NAIVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE



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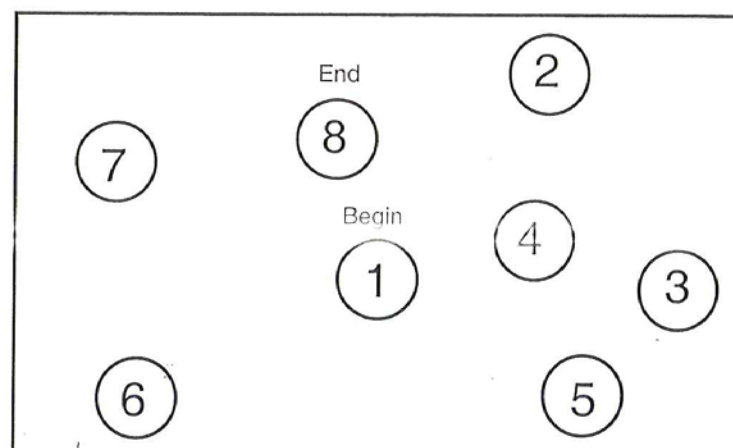
1/9.91

Code 4055 01 4

Appendix D Measures of Executive Functioning**Appendix D – 1 Trail Making Test****TRAIL MAKING**

Form 1, Part A

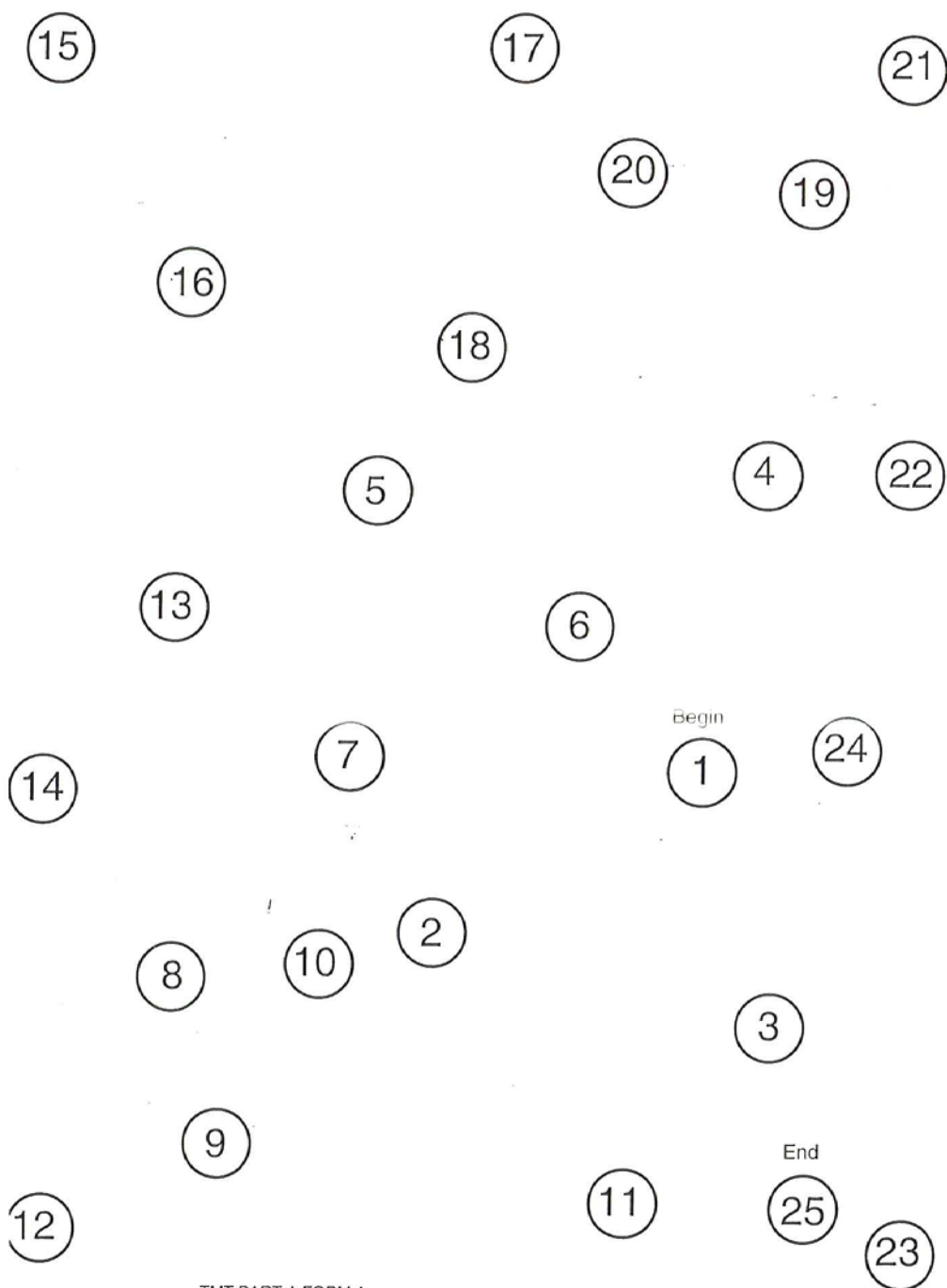
SAMPLE



DATE

TIME

NAME

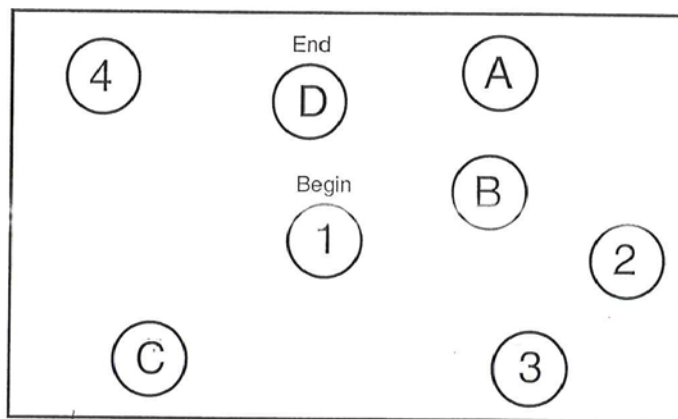


TMT PART A FORM 1

TRAIL MAKING

Form 1, Part B

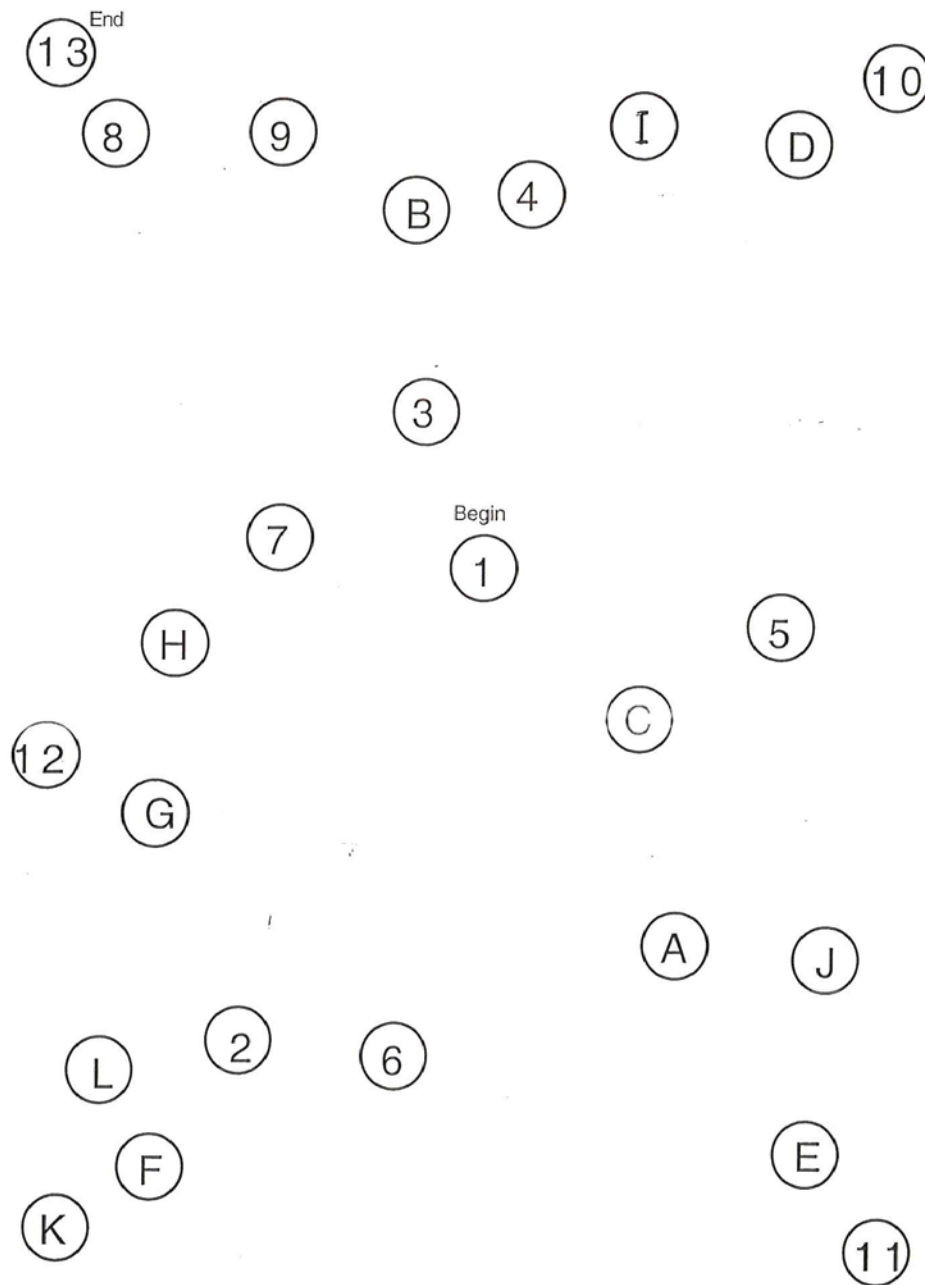
SAMPLE



NAME: _____

DATE: _____

TIME: _____



TMT PART B FORM 1

Appendix D – 2 Verbal Fluency Test**FAS TASK**

You will be told a *letter or category* and you must tell me as many words as you can that begin with that letter, excluding proper nouns (e.g., peoples' names, countries, towns etc.), numbers, and the same word with a different suffix (e.g. big, bigger, biggest). You have one minute for each letter. You should not repeat words. For example, if the letter is 'N', you could say 'Nasty', 'Natural' and 'Night'.

Practice Trial:

Can you give me three examples for the letter 'B'?

Test Session:

Tell me as many words as you can that begin with the letter:

F _____

_____**A** _____

_____**S** _____

_____**Animals** _____

Appendix E Hospital Anxiety and Depression Scale

Please read each item below and tick next to the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies, your immediate reaction will probably be more accurate than a long thought-out response.

<p>I feel tense or 'wound up' Most of the time A lot of the time From time to time, occasionally Not at all</p>	<p>I feel as if I am slowed down Nearly all the time Very often Sometimes Not at all</p>
<p>I still enjoy the things I used to enjoy Definitely as much Not quite so much Only a little Hardly at all</p>	<p>I get a sort of frightened feeling like 'butterflies' in the stomach Not at all Occasionally Quite often Very often</p>
<p>I get a sort of frightened feeling as if something awful is about to happen Very definitely and quite badly Yes, but not too badly A little, but it doesn't worry me Not at all</p>	<p>I have lost interest in my appearance Definitely I don't take as much care as I should I may not take quite as much care I take just as much care as ever</p>
<p>I can laugh and see the funny side of things As much as I always could Not quite so much now Definitely not so much now Not at all</p>	<p>I feel restless as if I have to be on the move Very much indeed Quite a lot Not very much Not at all</p>
<p>Worrying thoughts go through my mind A great deal of the time A lot of the time Not too often Very little</p>	<p>I look forward with enjoyment to things As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all</p>
<p>I feel cheerful Never Not often Sometimes Most of the time</p>	<p>I get sudden feelings of panic Very often indeed Quite often Not very often Not at all</p>
<p>I can sit at ease and feel relaxed Definitely Usually Not often Not at all</p>	<p>I can enjoy a good book or radio or television programme Often Sometimes Not often Very seldom</p>

Appendix F Adapted Autobiographical Interview Script (Studies 1 and 3)

First I want to tell you now a bit about the next task. We want to know how people remember events and experiences from their past, and how they imagine events which might happen in the future. To help with scoring, we will audiotape your responses. Over the course of the experiment you will be given 6 words, one at a time. There will be 2 conditions: a past and a future condition. We'll start with past/future condition.

Counterbalance which condition you will present first.

Pick which condition you will start with and the words you will use BEFORE the session.

a) Past Condition

So for the next 3 words you will need to remember a specific memory of a past event. It needs to have **occurred within the last 3 years**.

A few things to know about the memory you recall are:

- It must be an event you actually experienced.
- The event you describe must take place **over the course of less than one day** (e.g. describing a 3 week vacation would be wrong, but describing what happened on one specific day of that vacation would be correct).
- You have up to **three minutes to explore this memory**. However, you may not need the full three minutes but it is important that you recall as much detail about the event as you possibly can.
- We want you to try and **recall how you were thinking and feeling at the specific time the event took place**. Recall as many smells, sights and sounds that you remember.
- After recalling the memory after each word you will be asked a few simple questions before moving onto the next word.
- You will be given a **positive, a negative and neutral cue word**. If there is any word that makes you recalling a past memory, please let me know and we can move onto the next word.

Do you have any questions? Would you like an example of a response?

Provide one example if they need it. Offer a second if they want another one. Examples you can provide are as follows:

If you receive the word “BBQ”

“Last summer, I went to a BBQ at Gary’s place by the lake. It was a lovely sunny day and the lake looked beautiful. Before dinner we went out in the boat. Some of us also went swimming. We had a lovely dinner with steak and vegetable kebabs, and cake for dessert. I helped Gary clean up after dinner, while some other friends made a campfire. We roasted marshmallows on whatever twigs we could find in the yard, and sang songs while Gary played guitar.”

If you receive the word “Fur”, this may remind you of a specific memory of your cat. You could say:

“This word reminds me of my cat Tiger. I remember when I chose Tiger at the RSPCA. It was a cold overcast day and I remember the cages looking at all of the various cats. I remember this one grey cat curled up sleeping in the corner. It made me feel instantly protective towards this cat. I felt emotional because he reminded me of my childhood cat. I remember adopting Tiger and bringing him home with me. I bought him home in a box and he sat next to me in the passenger seat.”

Do you have any questions before we begin?

Introducing cue words **Please tell me as much and detailed as possible about a specific (positive/negative/neutral) event, happening in the last three years that involves the word Xxx.**

After each word have the participant complete the post interview questionnaire.

b) Future Condition

So for the next 3 words I want you to think about a **single event that might happen on a particular day in the future**. I want you to create or imagine or invent a scenario that **hasn’t happened to you before**. We are interested in how people imagine events which might happen in the future, so it needs to be something new to you, something that you have not previously-experienced. For the next 3 words you will be required to imagine an event which may occur in the future.

- It must be **no more than three years into the future**.
- This event must be one **that you may personally experience**.
- You can **be creative, but you cannot be totally unrealistic**, e.g. you can’t tell me

about going to the moon tomorrow

- The event you **describe must take place over the course of less than one day** (e.g. describing a 3 music festival would be wrong, but describing what will happen on one specific day of that festival would be correct).
- You have up to **3 minutes to explore this memory**. However, you may not need the full three minutes but it is important that you recall as much detail about the event as you possibly can.
- We want you to try and **imagine how you would be thinking and feeling at the specific time the event takes place**. For example, smells, sights and sounds that you can imagine.
- You will be given a positive, a negative and neutral cue word. If there is any word that makes you uncomfortable imagining a future scenario, please let me know and we can move onto the next word.

Do you have any questions? Would you like an example of a response?

Provide one example if they need it. Offer a second if they want another one.

You may receive the word “Peach”.

“I imagine a hot sunny day. I am with my two friends Sophie and Tess. We are sitting under a peach tree and we have set up a picnic, we have laid out a tartan rug and have opened a bottle of wine. Sophie has made a cheese and fruit platter. I feel very relaxed and happy because I have just finished my exams. The sun is on my back and it is making me very relaxed.”

If you receive the word “Vacation” (*only use this one if Vacation is not a cue word in the future condition*)

“Next week, I will be visiting Toronto, and I see myself doing some sightseeing around the city with my friend from Toronto, Sarah. At the end of the day, we decided to go to the CN Tower. I have seen the tower in the city before but I have never been up in the tower to see the view. We go up to the observatory deck to look at the view which is amazing, especially as the sun is setting. I take a photo of the view from different windows and we stand on a glass floor looking down at the ground.”

Do you have any questions before we begin?

Introducing cue words: **Please tell me as much and detailed as possible about a specific (positive/negative/neutral) event happening in the next three years that involves the word Xxx.**

Appendix G Modified Interview Script (Study 2)

Introduction of task

I'm going to ask you to imagine three vivid scenes in your mind's eye. So I'll give you a short description to set the scene and then I want you to take over and create as detailed a scene as you possibly can in your mind's eye, and describe it out loud to me.

I want you to give free reign to your imagination and to really try hard to picture the whole scene in your mind's eye as you're describing it. Give as much detail as you possibly can, not forgetting to use all your available senses including sight, sound, smell, everything. Be as vivid as possible; don't hold back! Remember, this is not about memory so don't just describe a memory you have. Instead we're interested in what you can visualize and imagine – ok?

Example

Let me give you an example to make sure you understand exactly what I want you to do. For instance, an example description might be: "Imagine you're sitting on a bench in a park. Describe the scene in as much detail as possible"

A response could be "The bench I'm sitting on is by a path on the grassy slope of a hill. It's a really sunny day on the warm summer's afternoon. There is not cloud and the sky is clear blue. Lying on the grass, a young good-looking couple are kissing. Further up the hill a boy is trying to fly a kite. There is a strong breeze and the colourful kite which is shaped as a dragon is soaring in the air. The boy is running and laughing happily. At the bottom of the hills is a large lake with trees lining it. I can see some people swimming in it and a barking black Labrador runs in after a stick making a splash. There are bees buzzing around and landing on flowers near my bench and there is sweet smell of grass and flowers. A jogger runs past smelling faintly of sweat, wearing a Walkman playing some loud rap music."

So do you see what I tried to do there? I included smells and sounds as well as lots of visual details. I was concentrating on imagining the whole scene in my mind almost as if I was really there. Don't worry if you find it difficult to begin with, or if your answer is not as detailed as mine; I've had a bit of practice! Do you have any questions?

Atemporal (Scene Construction)

Imagine you are sitting having a drink in a café. I want you to describe the experience and the surroundings in as much detail as possible using all your senses including what you can see, hear, and feel.

Narrative

I want you to listen and then I want you to take over and create a detailed short story as you possibly can in your mind's eyes, and describe it to me out loud to me. Give free reign to your imagination and really try hard to picture everything in your mind's eye as you're describing it.

Imagine you are standing in the middle of the impressive high vaulted entrance hall of an old castle. There is a tower somewhere in the castle, the top of which is accessed via a circular winding staircase. I want you to describe to me in as much detail as possible your route through the castle's many rooms and floors until you reach the top of the tower. Use all your senses including what you see, feel, and do on the way to the tower.

Self-Projection (Future Thinking)

I want you to imagine and describe something realistic that might actually happen to you. Imagine something you could be doing next summer, but just give me one event. I want you to describe that event and the surroundings in as much detail as possible using all your senses including what you can see, hear, and feel.

Appendix H Research Portfolio

Appendix H – 1 Confirmation of Study 1 Acceptance and Permissions

Psychopharmacology – Psych-2014-00329.R1: Paper accepted

20/12/14 5:44 PM

Psychopharmacology - Psych-2014-00329.R1: Paper accepted

on behalf of +oliver.howes+kcl.ac.uk@manuscriptcentral.com on behalf of oliver.howes@kcl.ac.uk

Sent: Saturday, 4 October 2014 11:03 PM

To: Kim Mercuri; Gill Terrell

04-Oct-2014

Manuscript No. Psych-2014-00329.R1

Title : Episodic foresight deficits in long-term opiate users

By: Mercuri, Kimberly; Terrett, Gill; Henry, Julie; Bailey, Phoebe; Curran, Helen; Rendell, Peter

Dear Dr. Mercuri,

We are pleased to inform you that your manuscript Psych-2014-00329.R1, entitled \"Episodic foresight deficits in long-term opiate users\", has been accepted for publication in Psychopharmacology.

The manuscript will now be forwarded to the publisher, from whom you will shortly receive information regarding the correction of proofs and fast online publication.

Should you have any questions regarding publication of your paper, please contact the responsible production editor, Ms. Journaliz Badon at Journaliz.Badon@springer.com.

Best wishes and thanks,

Dr. Oliver Howes

Principal Editor
Psychopharmacology

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Dec 29, 2014

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Licensed content title	Episodic foresight deficits in long-term opiate users
Licensed content author	Kimberly Mercuri
Licensed content date	Jan 1, 2014
Type of Use	Book/Textbook
Requestor type	Agency acting on behalf of other industry
Portion	Full text
Format	Print and Electronic
Will you be translating?	No
Print run	1
Author of this Springer article	Yes and you are the sole author of the new work
Order reference number	Published thesis
Title of new book	An Investigation of Episodic Foresight Ability in Users of Illicit Substances
Publisher of new book	Australian Catholic University
Author of new book	Kimberly Mercuri
Expected publication date of new book	Jan 2016
Estimated size of new book (pages)	200
Total	0.00 USD
Terms and Conditions	

Introduction

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Appendix H – 2 Confirmation of Study 2 Submission

Submission Confirmation

20/12/14 5:46 PM

Submission Confirmation

ees.dad.0.2d9aa9.bc2b4498@eesmail.elsevier.com on behalf of Drug and Alcohol Dependence
[DAD@jhmi.edu]

Sent: Sunday, 30 November 2014 12:37 PM

To: Kim Mercuri; Gill Terrett

Re: Deconstructing the nature of episodic foresight deficits associated with chronic
opiate use
Full Length Report

Dear Ms. Kimberly Mercuri,

Your submission entitled "Deconstructing the nature of episodic foresight deficits
associated with chronic opiate use" has been received by the journal Drug and Alcohol
Dependence.

You will be able to check on the progress of your paper by logging on to Elsevier
Editorial Systems as an author. The URL is <http://ees.elsevier.com/dad/>.

Your manuscript will be given a reference number once the Editor has been confirmed.

Thank you for submitting your work to this journal.

Kind regards,

Drug and Alcohol Dependence

Appendix H – 2 Confirmation of Study 3 Submission

CEN-OA 15-02 Submission Confirmation – Kimberly Mercuri

4/01/15 4:47 PM

CEN-OA 15-02 Submission Confirmation

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ncen-peerreview@tandf.co.uk

Sun 4/01/2015 5:37 AM

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To:kim.mercuri@acu.edu.au <kim.mercuri@acu.edu.au>; gill.terrett@acu.edu.au <gill.terrett@acu.edu.au>;

 1 attachment

Attached standard file: * CEN-Article-Publishing-Agreement.doc;

04-Jan-2015

Dear Miss Mercuri,

Thank you for submitting your manuscript entitled "Episodic foresight in regular cannabis users" to Journal of Clinical and Experimental Neuropsychology. It has been successfully submitted online and is with the editorial assistant awaiting further processing.

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Thank you again for submitting your manuscript to Journal of Clinical and Experimental Neuropsychology.

Sincerely,

Marie Pullan

Marie Pullan
Editorial Assistant

<https://pod51034.outlook.com/owa/projection.aspx>

Page 1 of 2

Appendix H – 3 Statement of Contribution for Study 1

Title: Episodic foresight deficits in long-term opiate users

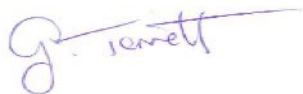
Status: Accepted for publication in Psychopharmacology.

I acknowledge that my contribution to the above paper is 50%.



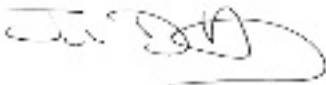
Kimberly Mercuri

I acknowledge that my contribution to the above paper is 20%.



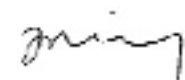
Associate Professor Gill Terrett

I acknowledge that my contribution to the above paper is 10%.



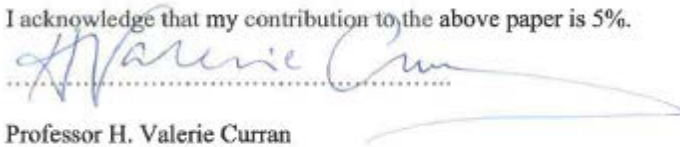
Associate Professor Julie Henry

I acknowledge that my contribution to the above paper is 5%.



Dr Phoebe Bailey

I acknowledge that my contribution to the above paper is 5%.

A handwritten signature in blue ink, appearing to read 'H. Valerie Curran', with a long horizontal flourish extending to the right.

Professor H. Valerie Curran

I acknowledge that my contribution to the above paper is 10%.

A handwritten signature in black ink, appearing to read 'Peter Rendell', with a long horizontal flourish extending to the right.

Professor Peter Rendell

Appendix H – 4 Statement of Contribution for Study 2

Title: Deconstructing episodic foresight deficits in long-term opiate users

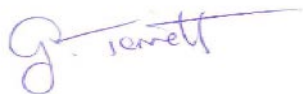
Status: Under review by Drug and Alcohol Dependence

I acknowledge that my contribution to the above paper is 50%.



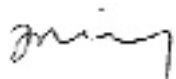
Kimberly Mercuri

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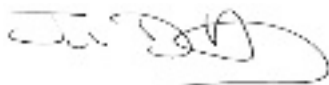
Associate Professor Gill Terrett

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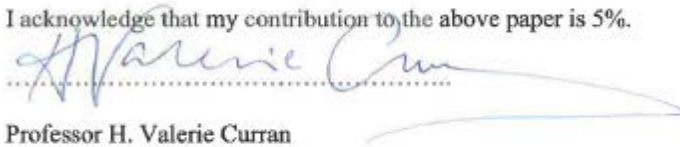
Dr Phoebe Bailey

I acknowledge that my contribution to the above paper is 5%.




Associate Professor Julie Henry

I acknowledge that my contribution to the above paper is 5%.

A handwritten signature in blue ink, appearing to read 'H. Valerie Curran', with a long horizontal flourish extending to the right.

Professor H. Valerie Curran

I acknowledge that my contribution to the above paper is 10%.

A handwritten signature in black ink, appearing to read 'Peter Rendell', with a long horizontal flourish extending to the right.

Professor Peter Rendell

Appendix H – 5 Statement of Contribution for Study 3

Title: Episodic foresight deficits in regular cannabis users

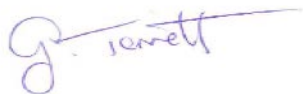
Status: Submitted for publication in Journal of Clinical and Experimental Neuropsychology

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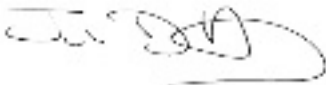
Kimberly Mercuri

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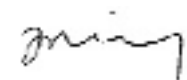
Associate Professor Gill Terrett

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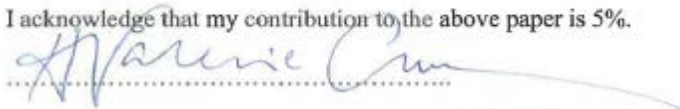
Associate Professor Julie Henry

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Dr Phoebe Bailey

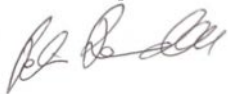
I acknowledge that my contribution to the above paper is 5%.



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Professor H. Valerie Curran

I acknowledge that my contribution to the above paper is 10%.



Professor Peter Rendell

Appendix H – 6 Conferences and Other Presentations

Mercuri, K., Terrett, G., Henry, J., Bailey, P. E., Curran, H. V., & Rendell, G. P. (2012).

Episodic future thinking deficits in illicit substance users. Poster presentation at the British Association of Psychopharmacology Summer Meeting Harrogate, United Kingdom

Mercuri, K., Terrett, G., Henry, J., Bailey, P. E., Curran, H. V., & Rendell, G. P. (2012).

Episodic foresight deficits in illicit substance users. Oral presentation at the Australian Catholic University Psychology Conference, Melbourne, Australia [Winner of Most Outstanding Oral Presentation]

Finalist – oral presentation ACU Three Minute Thesis Competition (2012) for presentation of Episodic foresight deficits in long-term opiate users

Winner – oral presentation ACU Three Minute Thesis Competition (2013) for presentation of Episodic foresight deficits in long-term opiate users

Finalist Trans Tasman Three Minute Thesis Competition (2013) for presentation of Episodic foresight deficits in long-term opiate users

Mercuri, K., Terrett, G., Henry, J., Bailey, P. E., Curran, H. V., & Rendell, G. P. (2014).

Episodic foresight deficits long-term opiate users. Poster presentation at the British Association of Psychopharmacology Summer Meeting Harrogate, United Kingdom

Mercuri, K., Terrett, G., Henry, J., Bailey, P. E., Curran, H. V., & Rendell, G. P. (2014).

Deconstructing episodic foresight deficits in long-term opiate users. Oral presentation at the Australian Catholic University Psychology Conference, Melbourne, Australia